TRACE RA is supported by Arthritis Research UK and the British Heart Foundation

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PROTOCOL APPROVAL – VERSION 5.0

TRACE RA trial: *TRial of Atorvastatin for the primary prevention of Cardiovascular Events in Rheumatoid Arthritis*

By signing this document I am confirming that I have read, understood and approve this protocol for the above study.

Chief Investigator Professor George Kitas	Signature	Date
Trial Statistician Dr Peter Nightingale	Signature	Date

TO BE SIGNED BY THE LOCAL PRINCIPAL INVESTIGATOR:

'By signing this document I am confirming that I have read this protocol and agree to abide by all provisions set forth therein. I agree to comply with the Medicines for Human Use (Clinical Trials) Regulations 2004.'

Principal Investigator (PRINT NAME)	Signature	Date

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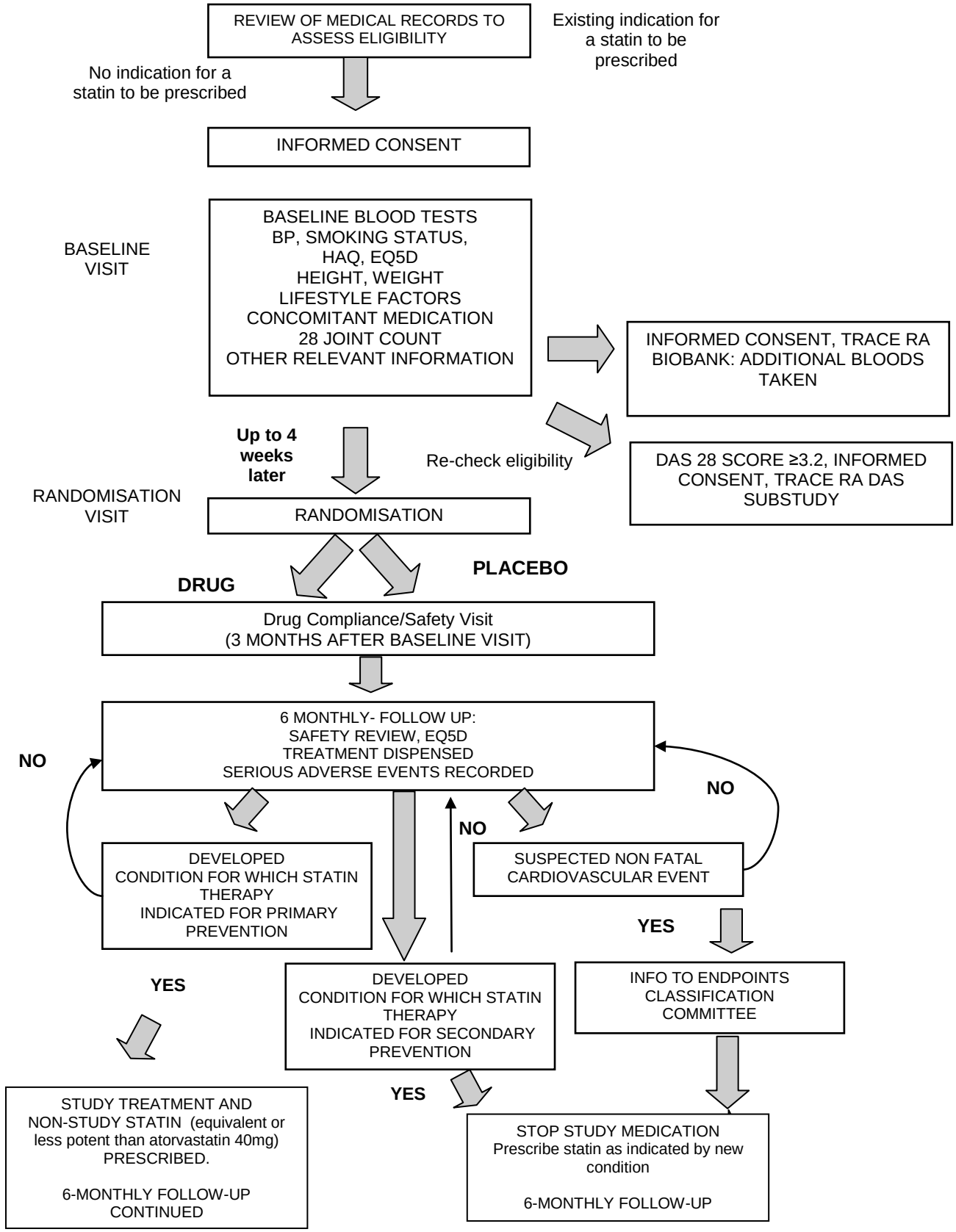

1. INTRODUCTION

Rheumatoid arthritis (RA) is associated with increased mortality from cardiovascular disease (CVD). This is thought to be due to accelerated atherosclerotic coronary heart disease (CHD), possibly occurring due to a combination of systemic inflammation augmenting an adverse cardiovascular risk profile.

Statins have a proven beneficial effect in reducing CVD events and mortality in at-risk populations, mostly due to their cholesterol-lowering properties, but also possibly through anti-inflammatory and immunomodulatory effects. Whether such benefit occurs in a high-grade inflammatory condition such as RA remains unknown, because such patients have been systematically excluded from previous statin trials.

This prospective, 5-year, multi-centre, randomised, double blind, placebo-controlled trial assesses the hypothesis that atorvastatin is more effective than placebo in the primary prevention of cardiovascular events in patients with RA*****. All patients receive lifestyle modification advice. Patients already receiving or requiring statin therapy for secondary prevention or whose managing physician thinks they should be on a statin for an existing indication will be excluded.

A nested sub-study *(TRACE RA-DAS)* investigates the hypothesis that atorvastatin is more effective than placebo as adjunctive therapy in reducing RA disease activity. Patients enrolled in *TRACE RA-DAS* have moderately or severely active disease at the time that they are recruited to the main study.

TRACE RA and TRACE RA DAS provide a unique opportunity to create a bio bank of appropriately timed DNA, RNA, plasma and serum *specimens (TRACE RA-BioBank)* that would allow assessment of important supplementary hypotheses in smaller sub-studies. These will, for example, investigate the hypothesis that environmental risk factors for RA and cardiovascular disease overlap and it is likely that there are shared genetic risk factors for the onset and progression of both conditions. A detailed analysis of the molecular markers associated with atorvastatin response in RA and in particular for investigation of inflammatory markers in RA at the level of the genome will also be possible. Whereas the creation of the bio-bank forms part of the current proposal, such sub-studies will be subject to detailed protocol formation and separate ethics approval in the future.

2. Background and Rationale

2.1 Trial Background

2.1.1 Cardiovascular disease mortality (CVD) and co-morbidity in RA

Rheumatoid arthritis (RA) affects about 0.8% of the adult population in the UK [1]. It is associated with significant disability and most of the efforts of the scientific community have concentrated on controlling inflammatory symptoms, minimising joint damage and improving function. It is less well appreciated that RA is associated with increased and premature cardiovascular (CV) mortality. This has not improved much over the last 3 decades, despite significant treatment advances. Almost half of all deaths in RA (and about 35-40% of the excess deaths) are due to cardiovascular disease (CVD) [2, 3].

The excess CV deaths in RA may be due to either an increased prevalence or increased case fatality of CVD in RA compared to the general population, and there is now evidence for both of these. Overall CVD (including individual risk factors such as hypertension and dyslipidaemia) is the commonest co-morbidity in patients with RA [4, 5]. Although rheumatoid heart disease is common on echocardiography or autopsy it rarely causes haemodynamic upset, so is an unlikely cause of death [6]. Instead, the evidence suggests that the main cause of increased CV death in RA is ischaemic heart disease (IHD). Mortality studies show that most CV deaths in RA are due to ischaemic pathologies such as myocardial infarction (MI) or congestive heart failure (CHF); probably due to accelerated atherosclerotic coronary heart disease (CHD) [reviewed in 2, 3]. Indeed, functional and phenotypic surrogate markers for atherosclerotic CHD, such as endothelial dysfunction [7], increased carotid intima-media thickness [8, 9] and changes in arterial elasticity [10] are commoner or more pronounced in RA patients than in controls, as are serological surrogates such as coagulation abnormalities [11-14]. The outcome of acute coronary syndromes is also worse in RA than matched controls [15, 16], probably due to increased instability of atherosclerotic plaques and enhanced stress responses [17] associated with high-grade systemic inflammation characteristic of RA.

It is now accepted that atherosclerosis, like RA, is a chronic inflammatory condition [18]. Immunohistochemical studies suggest significant similarities between the mechanisms responsible for chronic synovitis and damage in the rheumatoid joint and the generation and rupture of the atherosclerotic plaque in the vasculature, including the cellular infiltrates adhesion molecule expression, cytokine millieux, free radical and degradative enzyme release [reviewed in 19-21]. This is further supported by epidemiological work in the general population showing that several serological markers of systemic inflammation may associate with cardiovascular outcomes. The best studied is CRP, the level of which, even within the normal range, is a good predictor of future MI or ischaemic stroke in the general population, whether there is pre-existing CVD or not [22, 23]. Baseline CRP is also a predictor of CVD death in patients with early inflammatory arthritis, even within 5 years from the onset of arthritis [24]. RA disease activity as assessed by the erythrocyte sedimentation rate, raised fibrinogen levels [25], joint swelling [26] or a composite score [27] has been shown to associate with CV events, CV death and overall mortality respectively.

2.1.2 The effect of current treatments on CVD risk and outcome in RA

Thrombotic variables may be positively or negatively affected by commonly used medications, particularly non-selective non-steroidal anti-inflammatory drugs (nsNSAIDs), cyclo-oxygenase 2 inhibitors (Coxibs) and antimalarials. The effects of other treatments for RA are less clearly defined: disease-modifying anti-rheumatic drugs (DMARDs) do not appear to increase overall mortality; in contrast, effective control of inflammatory activity appears to confer survival benefits [28-31]. However, it remains to be proven whether such benefits are due to improved CV outcomes, and although suppression of inflammation in RA makes good theoretical sense, we still do not know how to achieve it – and in which patients – without compromising the vasculature. For example, compared with other DMARDs, the use of methotrexate (MTX) in RA has been reported in one study to associate with reduced overall and CVD mortality in unselected patients [28], probably due to superior control of inflammation. In another study however, use of MTX in RA patients with pre-existing CVD led to a significant increase in mortality compared with other DMARDs [32]; this may be due to its anti-folate, thus potentially hyperhomocystinaemic effects [33]. Also, use of anti-TNF or potent anti-inflammatory/immunosuppressive therapy, although effective at reducing systemic inflammation, may [34] or may not [35, 36] associate with improvements in vascular function and surrogates of atherosclerosis. This emphasises the need for prospective, randomised, controlled trials to confirm any theoretical predictions.

2.1.3 Classical cardiovascular risk factors in RA

Inflammation in RA may affect classical CVD risk factors, including lipid metabolism. Dyslipidaemia has been well documented in RA and appears to associate with the acute phase response [37]. Most studies suggest that during active RA, total and LDL cholesterol may be reduced, but HDL is consistently found to be even further reduced leading to an unfavourable lipid profile. Control of disease activity with several drugs or use of ciclosporin may lead to elevation of all lipid levels with the lipid profile remaining unfavourable.

Generally, RA patients have a higher prevalence of vascular risk factors [38] and signs of asymptomatic arterial disease [39] than matched controls, which may be present even before the onset of inflammatory polyarthritis [40]. About a third of unselected hospital RA patients have documented CVD and/or CVD risk factors and are on treatment for these. Of the remaining two thirds, 90% have at least one modifiable risk factor. 70% and 60% have above the recommended levels of total cholesterol and systolic blood pressure respectively, and 40% have a >15% 10-year risk of a CHD event [13, 41]. Smoking, obesity and sedentary lifestyle may be important but are also more difficult to modify in RA than in the general population, due to the physical and psychosocial consequences of the disease [42]. As occurs in other high-risk groups (e.g. diabetes), pharmacological interventions targeted at hypertension and/or dyslipidaemia may be the most practical approach to this problem. Hypertension in RA may associate with the use of NSAIDs and Cox-2 inhibotors. Theoretically, ACE inhibitors (ACE-I) may have particularly beneficial effects in RA, since they have been shown to confer significant benefits in other high-risk populations [43], may have anti-oxidant properties and improve endothelial dysfunction [44]. However, other co-morbidities, polypharmacy, frequent treatment changes and the age groups characteristic of RA make both the routine use of such drugs problematic: for example, the combination of NSAIDs and ACE-I is commonly nephrotoxic, particularly in the elderly [45].

2.1.4 Statins

Statins have a combination of properties that makes them particularly attractive for CV outcome studies in RA: they can be delivered in single daily dosing (an important factor in patients receiving multiple medications); they do not require much monitoring over and above that usually necessary for RA patients on DMARDs, and they do not interact adversely with most of the treatments commonly used in RA.

The efficacy of statins in the primary and secondary prevention of CHD events in the 'at risk population' has been demonstrated in several trials, with a reduction of major coronary events of 35% or above [45-51]. This is related almost exclusively to their lipid-lowering effects. There is however evidence from human *in vivo* studies, animal models and *in vitro* work, which suggest that statins have several other, so called "pleiotropic" effects. These include: reduced oxidative stress, anti-inflammatory and immunomodulatory actions, improved endothelial function, beneficial effects on vascular smooth muscle cells, antithrombotic effects and even antihypertensive properties. Several of these pleiotropic effects of statins are relevant to the atherosclerotic and chronic inflammatory pathologies of RA [52-57]. This opens up the possibility that statins may be beneficial to the rheumatoid component of RA [58, 59]. Indeed, the TARA trial [60], a 'proof of principle' trial demonstrated that atorvastatin 40mg daily, as an adjunct to DMARD therapy, provided additional benefit for inflammatory control of RA in at least a subgroup of patients.

With the exception of ciclosporin (which is metabolised through cytochrome P450 and can thus increase the risk of myopathy when used with some statins) there are no known significant interactions between anti-rheumatic drugs and statins. Statins are useful for secondary and primary prevention, in patients with overt CHD or those with a 10-year CVD (CHD+stroke) risk of >20%. Recent work shows that this is the case also for low risk patients, e.g. patients with diabetes with a <15% CHD risk [61]. Whereas many statin-effects may be class effects, there is evidence to suggest individual differences. Atorvastatin appears suitable for this pragmatic study. Several studies have shown a good safety profile over a wide dose range with no need to adjust dose for renal impairment. Improvements in cardiovascular end-points have been shown in many different settings and clinical populations such as ACS, stable CHD, diabetes and hypertension, including low CV risk diabetics. Early benefits seen in some atorvastatin studies have not been seen with other statins, particularly simvastatin, whereas newer statins (e.g. rosuvastatin) currently lack a large body of endpoint data. Atorvastatin may also have better effects on plaque progression and inflammatory marker reduction than either pravastatin or simvastatin [62-68]. Atorvastatin is also the only statin that has been used in an RA population with some "proof of concept"

that, at a dose of 40mg daily, it can reduce systemic inflammation and improve lipid profile in RA [60], and has been shown to reduce arterial stiffness in patients with RA [69].

2.2 Rationale

2.2.1 Need for the trial

Cardiovascular morbidity and mortality in RA are common, severe and have not received adequate attention until very recently. No trials to date have addressed whether any intervention(s) can reduce the rate of CV events in patients with RA. Articles in leading medical journals, such as the Lancet [70] clearly identify the need for sufficiently powered and specifically designed trials addressing this problem.

The cause of the CV morbidity and mortality in RA is probably multifactorial, and may be best treated by a drug with pleiotropic effects in addition to standard lipid lowering. The proposed intervention is based on sound basic science and extensive clinical trial data in other populations. However, the efficacy and safety of such an intervention remains to be proven in the RA population which, due to its major morbidity, polypharmacy and concomitant muscle pathology has been systematically excluded from all major statin trials.

2.2.2 Aim of the trial

TRACE RA aims to establish whether treatment with atorvastatin will protect patients with RA aged ≥50 years or with ≥10 years' duration of RA from fatal and non-fatal atherosclerotic events.

A nested sub-study ***(TRACE RA DAS)*** has been designed to determine whether atorvastatin, used in conjunction with standard DMARD therapy, will provide added arthritis control in patients with moderately or severely active RA.

A further sub-study, (***TRACE RA BioBank)*** has also been incorporated into the main study. The aim of this sub-study is as follows:

1. To develop a DNA, plasma and serum repository from all patients consenting to the biobank from within those enrolled in the main TRACE RA study in centres where such blood preparation is possible, and the centres agree to provide such samples.
2. To develop an RNA, serum and plasma repository for gene expression profiling from TRACE RA DAS subjects with sampling at baseline and at 6 months.

2.2.3 How the results will be used

If effective, the implementation of this intervention in the routine rheumatology clinic would be easy and, apart from the drug costs, would have no resource implications.

The trial will increase awareness of CV morbidity and mortality in RA and, in the process, identify patients who need to be properly risk-assessed and treated.

If atorvastatin also shows evidence of being a disease-modifying drug this will add to the choice of such drugs, which is at present limited. Current evidence suggests that the goal in RA treatment should be to minimise the inflammatory response – ideally aiming for remission. This is likely to slow or halt radiographic progression and to improve cardiovascular co-morbidity and mortality. All additions to the family of drugs which reduce inflammation are welcome.

3. Trial Design

Trial type
Multi-centre, randomised, double blind, placebo-controlled trial

Primary hypotheses
TRACE RA – All patients: Atorvastatin is more effective than placebo in the primary prevention of cardiovascular events in RA patients.

TRACE RA DAS patients only: Atorvastatin is more effective than placebo as adjunctive therapy for the reduction of disease activity in RA patients

3.1 Primary endpoints

TRACE RA (all patients): Primary endpoints
The primary comparison will involve Cox regression analyses of "major vascular events" (defined as non-fatal myocardial infarction, non-fatal presumed ischaemic stroke, transient ischaemic attack, any coronary or non-coronary revascularisation or cardiovascular death excluding both confirmed cerebral haemorrhage [ICD I64-99 in the 10th International Classification of Diseases]) and non-coronary cardiac death [ICD I00-I15 and I26-I52] during the scheduled treatment period among all those allocated atorvastatin tablets versus all those allocated placebo tablets (i.e. "intention-to-treat" comparisons).

TRACE RA-DAS (*sub-study only)*:
EULAR moderate or good response based on DAS 28 at 6 months

3.2 Secondary and tertiary endpoints

TRACE RA secondary endpoints
Components of the primary endpoint separately:

- Coronary events
- Presumed ischaemic stroke or TIA;
- Any arterial revascularisation
- Cardiovascular death excluding both confirmed cerebral haemorrhage [ICD I64-99 in the 10th International Classification of Diseases]) and non-coronary cardiac death [ICD I00-I15 and I26-I52]

TRACE RA tertiary endpoints
Total and cause-specific mortality (coronary, other vascular and non-vascular death separately)
Hospitalisations for various other causes
Statin safety-related outcomes (persistent elevation of ALT or AST; myopathy (defined as muscle symptoms plus CK>10 x upper limit normal)
Differences in lipid levels during follow-up in a random sample
Functional outcome assessed by HAQ and EQ5D

Allowance for multiple hypothesis testing in these analyses will be made using the "Bonferroni" correction.

TRACE RA-DAS secondary endpoints
DMARD (Disease Modifying and Anti-Rheumatic Drugs) changes
DAS 28 at month 12 and 24.
Functional outcome assessed by HAQ and EQ5D at month 6, 12 and 24.

3.3 Trial intervention

Active treatment: Atorvastatin 40mg once daily with **Placebo** consisting of dummy atorvastatin once daily (both provided by Pfizer UK Ltd). All patients are counselled about modifiable cardiovascular risk factors at screening visit.

4. Study Organisation

TRACE RA aims to randomise up to 5350 RA patients, from up to 120 centres in the United Kingdom (UK). The aim is to continue recruitment until the required number of participants has been recruited to accrue sufficient person years of follow-up to achieve study power (see Section 10). The study commenced in August 2007, and recruitment is currently planned to continue until March 2014, with completion of follow up currently planned for March 2016.

The Chief and Lead Investigators plus the Trial Manager form an executive trial core management committee (TCMC). There are trials units based in Dudley, Dundee and Manchester, which oversee the management of this trial according to ICH GCP. The trials units support their affiliated recruiting centres and monitor data management for the trial. Each recruiting centre agrees affiliation to one of the trials units prior to participating in the study. However, it may be necessary to make some changes during the trial to balance the workload between trial units.

Data from all recruiting centres are being collected at the AR UK Epidemiology Unit, University of Manchester, who maintain overall responsibility for all trial data, and for the Standard Operating Procedures (SOPs) that describe how the trial is to be conducted within participating trials centres and units. All data are handled, computerised and stored in accordance with the Data Protection Act 1998. Quality control of data is maintained by the University of Manchester through regular meetings to discuss data management with the other trials units. The trials units (Dudley, Dundee and Manchester) are responsible for checking case report forms (CRFs) for compliance with the protocol, inconsistent and missing data, and for resolving data queries.

Data and statistical analysis is overseen by the Trial Statistician, Dr Peter Nightingale, who is based at the Wellcome Trust Clinical Research Facility in Birmingham.

5. ELIGIBILITY CRITERIA

Inclusion criteria:

- Patients who satisfy 1987 ACR classification criteria for RA applied cumulatively [71]
- Age ≥50 years ***OR*** RA disease duration ≥10 years
- Written informed consent

Exclusion criteria:

- Already taking a statin
- Known cardiovascular disease deemed to require statin therapy

  i.e. previous episodes of confirmed Acute Coronary Syndrome (ACS), unstable angina; myocardial infarction with or without ST elevation; or stable CHD/CVD deemed to require statin therapy on clinical grounds, including:

  → Previous amputation due to severe peripheral vascular disease or current peripheral arterial disease

  → Previous central or peripheral revascularisation procedure (including angioplasty or stent, artery bypass graft surgery)

  → Accelerated hypertension, severe heart failure (class III or IV), significant dysrhythmia or angina requiring hospitalisation in the 6 months preceding potential study entry

  → Uncontrolled hypertension (treated or untreated) defined as systolic blood pressure > 200 mmHg and/or diastolic blood pressure > 110 mmHg (identified as the disappearance of all sound (Korotkoff Phase V) after sitting quietly for at least 3 min)

  → Previous cerebrovascular accident

  → Other accepted indication for statin therapy according to the investigator's current clinical practice

- Diabetes
- Regular use of contra-indicated drugs – see below:

Contra-indicated drugs:

Statins:

Atorvastatin (Lipitor), Fluvastatin (Lescol), Lovastatin (Mevacor), Pitavastatin (Livalo), Pravastatin (Lipostat), Rosuvastatin (Crestor), Simvastatin (Zocor),

Other contra-indicated drugs:

e.g. amiodarone, azole anti-fungals (fluconazole, ketoconazole, itraconazole), ciclosporin, fibrates, HIV protease inhibitors, macrolide antibiotics (erythromycin, telithromycin, clarithromycin), niacin, veramapil

Drugs known to affect lipid levels

e.g. colestipol, ezetimibe

Other exclusions:

- Primary muscle disease or CK >3 x ULN
- Known familial hyperlipidaemia

- Acute liver disease
- Severe renal dysfunction (Stage 3 or 4) or creatinine > 200 micromol/l or receiving renal replacement
- Uncontrolled hypothyroidism
- Hypersensitivity or intolerance to statins
- Pregnant, breast feeding or of child bearing potential not using adequate contraception*
- Alcohol abuse
- Participating in another Clinical Trial of Investigational Medicinal Product (CTIMP)
- Drinking more than 240ml of grapefruit juice per day
- Any other serious illness that may compromise safety or trial compliance

*Adequate contraception for the purpose of this trial will include the following:

Barrier Method:
Male condom
Female condom
Contraceptive Diaphragm
Cervical cap
Contraceptive Sponge
Diaphragm cleaning
Vaginal Spermicide
Intrauterine Devices

Endocrine Method:
Combined oral contraceptives
Minipills
Injectable progestins
Implantable progestins

Surgical Sterilization
Female sterilization
Male sterilization

6. TRIAL PROCEDURES

6.1 Patient selection and informed consent

Once a patient has been selected based on the eligibility criteria, sufficient time is provided for the patient to decide on trial entry, but the time which elapses between randomisation and start of treatment should be minimised (ideally no longer than four weeks).

Potentially eligible RA patients are identified from their medical records based on the presence of inclusion/exclusion criteria using the Trial Screening Form. Information on the trial is given to potentially eligible patients and they are asked to give their written informed consent. Patients are checked to ensure they are not already on a statin and do not have an existing indication for a statin according to standard clinical practice.

The Registration Form is faxed to the Manchester TRACE RA Office within 24 hours of registering a patient to the trial. A schedule of the patient's visits ('PCA' – Patient Clinical Assessments) is sent to the recruiting centre to confirm receipt of the registration form.

All other documents (copy of consent forms, baseline data ('baseline/randomisation' form'), questionnaires, eligibility checklists) should be posted to the Manchester TRACE RA office within 7 working days.

Trial ID numbers are provided on pre-printed Patient details logs – a trial number from the CRF used for each patient is the patient's trial number for the duration of the trial.

6.2 Trial investigations:

(Please see Appendix 10 for Trial Evaluation Schema)

Local routine practice is followed with regards to screening for 10 year cardiovascular risk. Recruiting centres that routinely screen for CVD risk continue to do so and those that do not continue to not screen. Therefore there is no requirement to measure the lipid profile of patients prior to trial entry in centres that do not routinely measure patients' CVD risk. Where a centre routinely measures CVD risk, we recommend that the JBS2 risk calculator is used (http://www.bhsoc.org/Cardiovascular_Risk_Charts_and_Calculators.stm)

6.2.1 Baseline/randomisation visit

Patients are given the opportunity to ask any questions they may have, and then asked to provide their written informed consent to enter the study.

- **Following this the patient has the following recorded:**
  - → Medical history
  - → Smoking status
  - → Record of concomitant medication
  - → DAS 28 tender and swollen joint counts
  - → Height, weight and blood pressure

- **Participants are asked to complete the following questionnaires:**
  - → Patient global assessment (VAS)
  - → HAQ [72] and EQ5D [73] questionnaires
  - → Lifestyle factor questionnaire

- **And asked to give a blood sample:**
  - → ESR and/or CRP tests: if results are available from within the last 6 weeks while their treatment has remained unchanged and the patient is stable then these results may be used instead;
  - → RhF (rheumatoid factor) and/or anti-CCP (anti-cyclic citrullinated peptide antibody): if results are available from previous points during the course of their RA, then these results may be used instead.

  All patients are also asked to consent to the optional TRACE RA BioBank sub study (Appendix 2).

- ***For TRACE RA-BioBank sub study participants (Optional)***
  → 2 x 10mls plasma blood sample
  → 2 x 10mls serum (clotted) blood sample
  → 2 x 10mls EDTA blood sample (for DNA) (immediately stored at -80°C)
  → 1 x 4.5mls plasma (citrate) blood sample

  Patients who have a DAS28 score of ≥3.2 may be asked to consent, in addition, to the TRACE RA DAS sub study (Appendix 1). The DAS28 (Disease Activity Score) [74] will be calculated using the most recent ESR/CRP. Outcome measures will be recorded in the CRF and patient hospital notes (See Appendix 6). **This sub study will only be run at selected centres**.

- ***For TRACE RA DAS sub study participants (Optional)***
  → Nurse global assessment (VAS)
  → Bloods taken as for the Biobank study (as outlined above) PLUS
  → 4 x 2.5mls blood sample (for RNA testing) on two occasions (baseline and 6 months)

All patients are counselled by the study nurse or doctor about modifiable cardiovascular risk factors, e.g. smoking or obesity (BMI>30kg/m^2) and given a copy of a leaflet prepared for the TRACE RA trial. GPs are informed of all significant clinical issues found at the screening visit using a standard letter.

Patients are then randomised to either the atorvastatin arm (40mg of atorvastatin oral tablet taken once daily) or placebo arm (placebo atorvastatin oral tablet taken once daily) of the trial. The patient is also registered with the trials units in order to obtain confirmation of the trial number for analysis of their medical information and subsequent dispatch of the trial drug.

6.2.2 Allocation of patients to trial treatment arm

Allocation of patients to trial treatment arm: The study is double blind with matching placebo. Neither patients, investigators nor trial units are aware of the treatment allocation. The medication is provided by Pfizer UK Ltd., bottled by an independent pharmaceutical company (Catalent Pharma Solutions UK Limited) to GMP standards and dispensed by the local study pharmacist. The randomisation process is incorporated into the drug labelling. Each patient is allocated a filled and labelled bottle coded with a unique drug number when entering the trial. All future supplies for this patient will be coded with the same unique drug number. Patients will continue on the same treatment (i.e. active or placebo) throughout the duration of the study. Scratch cards are supplied to the local pharmacy so that the code can be broken if necessary**.** Catalent Pharma Solutions provides the independent trial statistician with information about treatment allocation by unique drug number to enable the interim analyses to be conducted. A TRACE RA Standard Operating Procedure is in the study site file for further information on providing treatment to patients.

6.2.3 Follow-up visits for TRACE RA participants

Patients are asked to attend visits at **3 months**, and then **6-monthly from randomisation**. When attendance is not possible the CRF may be completed by telephone interview, however, every effort will be made to have an actual attendance to clinic at least once a year - in many cases this may coincide with the patient's routine clinic visit appointment. If patients are to continue study treatment, preferably ALT (and if ALT not available then AST) measurements are mandatory within **6 weeks** of the follow-up visit - the overwhelming majority should be available through the patient's routine DMARD monitoring.

- **Month 3 from first administration of trial drug**

Every effort will be made to conduct this review appointment by clinic visit, but in exceptional circumstances it could be done by telephone interview. During this 3-month review appointment: (a) Actively seek whether muscle symptoms have occurred: **if** NEW and SIGNIFICANT muscle pain or weakness have occurred then measure contemporary ALT*/AST and CK; (b) Record any serious adverse event (including any possible cardiovascular event - please see Appendix 5 for definition of cardiovascular event and Section 9 for detailed definitions of SAEs) and record length of any in-patient stay, whether for elective/planned procedures or not; (c) Review ALT/AST result: if ALT/AST available from within the last 6

weeks while patient was taking study treatment, other treatment was stable, and no new and significant muscle symptoms have been reported, then this value may be accepted and recorded in CRF with the date measurement was done; if ALT/AST not available within the last 6 weeks then request test and review result before advising patient whether they should / should not continue on study medication. (d) Record current relevant medication.

- **6- monthly from randomization**

Follow-up may be conducted either by attendance at clinic or by telephone interview, but every effort will be made to have one clinic review appointment per year. During these 6-monthly reviews act as above (3-month review) but also record HAQ and EQ5D annually since randomisation.

In the presence of new and significant muscle symptoms:

(a) if CK>10xULN, then stop trial medication - not to be restarted.

(b) if ALT/AST<2xULNand CK<3xULN, trial medication can be continued with clinical follow-up. Further measurements of ALT/AST and CK can be requested if thought to be necessary by managing rheumatologist.

(c) if ALT/AST >2xULN and/or CK between 3-10xULN retest in 1-2 weeks: (c1) if normalisation has occurred to ALT/AST<2xULN and CK<3xULN then act as per option (b) above; (c2) if CK>10xULN stop trial medication; (c3) if ALT/AST>2xULN and CK again between 3-10xULN retest in 1 week: if elevation persists then stop trial medication.

In the absence of any new and significant muscle symptoms:

In general, if abnormalities of LFTs with atorvastatin are to occur, they are more likely to occur within the first 3-6 months of treatment. After that, any DMARD or non-steroidal therapy (or other medications) would be a more likely cause of LFT abnormalities and the managing rheumatologists should consider stopping these drugs prior to stopping the trial medication. Attribution of LFT abnormalities to the trial medication or anti-rheumatic drug is left to the managing rheumatologist, but the TRACE RA team, including the Chief and Lead Investigators or delegated person could advise, if necessary.

If LFT abnormalities are thought to be attributable to anti-rheumatic medication rather than trial drug: then follow usual rheumatology practice guidelines (e.g. BSR monitoring guidelines).

If LFT abnormalities are thought to be attributable to trial drug rather than other reasons:

(a) If ALT/AST within normal range or <2xULN, then continue trial medication and arrange next follow-up.

(b) If ALT/AST between 2-3xULN then continue trial medication and retest in 1 week. (b1) if normalisation to <2xULN has occurred, then act as per option (a) above. (b2) if ALT/AST persists at between 2-3xULN or more, then temporarily stop trial medication and act as per option (c) below.

(c) If ALT/AST>3xULN continue trial medication and retest one week later: (c1) if ALT/AST has recovered to <2xULN then continue trial medication and act as per options (a) above; (c2) if ALT/AST between 2-3xULN then retest in 1 week and if ALT/AST persists at between 2-3xULN or more, temporarily stop trial medication and act as per option (c3); (c3) if ALT/AST elevation persists at >3xULN then temporarily stop trial medication and retest in 3 weeks: (c3i) if normalisation has occurred, then act as per options (a) or (b), whichever applies; (c3ii) if abnormality persists at >3xULN then stop trial medication – not to be restarted.

*If ALT and AST are both available in a local hospital then ALT is to be preferred for liver monitoring since it is more liver specific than AST.

<u>Follow-up visits for TRACE RA DAS participants</u>

- ***Month 6 from first administration of trial drug (TRACE RA DAS sub-study only)***
  Patient Global Assessment (VAS)
  Nurse Global Assessment (VAS)
  28 tender and swollen joint count
  ESR and/or CRP
  → 4 x 2.5mls blood sample (for RNA analysis)
  → 2 x 10mls plasma blood sample

→ 2 x 10mls serum (clotted) blood sample
→ 1 x 4.5mls plasma (citrate) blood sample

→ ***Month 12 from first drug administration of trial drug (TRACE RA DAS sub-study only)***
Patient Global Assessment (VAS)
Nurse Global Assessment (VAS)
28 tender and swollen joint counts
ESR and/or CRP

- ***Month 24 from first administration of trial drug (TRACE RA DAS sub-study only)***
Patient Global Assessment (VAS)
Nurse Global Assessment (VAS)
28 tender and swollen joint counts
ESR and/or CRP

Patients in the TRACE RA DAS sub-study have a mandatory visit at 6 months at which the components of the DAS28 score are checked. Consultants are asked not to change the DMARD therapy of patients enrolled in the disease activity sub-study for the first 6 months of the clinical trial.

Additional visits to the rheumatology clinic and changes in medication will be decided based on clinical need. Patients will be given the telephone number of their consultant or Rheumatology department/helpline in case they have any concerns whilst enrolled on the trial.

Patients will continue the intervention for the entire period of their participation in the trial, unless the trial steering committee decides to discontinue the study for any reason. Any patients who discontinue the intervention will remain under follow up.

6.3 Procedure for unblinding

Each hospital pharmacy has a nominated person who can break the randomisation code for an individual patient if required in a medical or other emergency. The code (scratch card) for each individual patient is kept securely in the pharmacy. The local and main co-ordinating centre is informed each time the code is broken and is given the reason for the unblinding.

6.4 End of trial

The trial is currently planned to continue recruiting until March 2014 with the last follow-up appointment being in March 2016, or until a sufficient number of events has accrued to provide statistical power (currently calculated to be around 370 confirmed primary events) whichever is the earlier. All patients will be followed-up (by phone or attendance) 6-monthly until the trial has been completed and will stop their medication on the day of their final assessment. All events which occur prior to this final assessment will be included in the analysis whether or not the patient has continued to take the trial medication. Because of the 'intention-to-treat' (ITT) analysis, it is essential to follow all patients (including those that have reached a trial endpoint) up to this 'final assessment' date.

7. DISCONTINUATION OF STUDY MEDICATION

Patients who experience a cardiovascular event will stop their study medication and take statin prescribed by their managing doctor. They will continue to be followed-up. Patients who, during the course of the trial, develop other indications for statin therapy (e.g. diabetes) can continue on the trial medication AND be prescribed unblinded statin, preferably atorvastatin up to a maximum dose of 40mg daily, or an alternative statin up to a maximum dose equivalent to atorvastatin 40mg daily. If a higher dose than this is required then the trial medication will be stopped and an unblinded statin prescribed. A record of any concomitant statin prescription will be made on the CRF. All patients will also continue to be followed-up in the trial.

If the trial is stopped early for safety reasons, all patients will stop the study medication. If it is stopped early due to efficacy of the statin arm, all patients will be offered the opportunity to continue/commence statin therapy. If the trial goes its full length, all patients will stop the trial medication and be managed according to their physician's preference pending full analysis and publication of the trial findings.

Patients are free to withdraw from the trial treatment at any point. This will have no implications on their future care.

Breaks in study medication: Should patients take a break in their study medication, they may re-commence at any time provided /ALT/AST is within the screening limits within the last 6 weeks and other treatment has remained stable. ALT (or AST if ALT not available) should be checked 3 months after restarting study drug.

8. DRUG SUPPLIES AND LABELLING

Atorvastatin and the placebo atorvastatin are supplied free of charge by Pfizer UK Ltd.

8.1 Packaging and labelling of study medication

The drug is packaged in bottles and labelled by Catalent Pharma Solutions according to GMP standards. Bottles are labelled with a minimum of the following information:

- Unique drug number (number allocated to drug bottle)
- Packaging lot number
- Expiry date
- Number of tablets in bottle
- Dosage instructions
- Storage conditions

Bottling and labelling will be done in several runs spaced throughout the trial. All bottles contain extra tablets to allow for delays in patient visits.

8.2 Supply of study medication to centres

Catalent Pharma Solutions supplies the packaged drugs to the pharmacies of individual hospitals at regular intervals throughout the trial.

Patients are asked to return any unused medication to pharmacy which will be destroyed on site.

Patients are provided with a 6 monthly supply of the study medication. At the first visit they are advised that they must attend for a safety visit at 3 months and should only continue the medication beyond this point if advised to do so. Each time that the trial drug is dispensed, the pharmacy will be asked to affix the supplementary drug label to the prescription sheet so that a 'dispensing record' can be maintained.

9. PHARMACOVIGILANCE

9.1 Cardiovascular Outcomes and reporting of cardiovascular outcomes

Any **cardiovascular event** or endpoint experienced by a patient should be reported on the **serious adverse events form** that is provided in the site file, as these events will be classified as part of the endpoints of the trial. All information regarding a cardiovascular event should be faxed to the AR UK Epidemiology Unit at the University of Manchester on **0161 275 5043 within 24 hours** of knowledge of the event. The local principal investigator or research nurse will be contacted by the trials unit if further information is required.

9.2 Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) is defined as *any untoward medical occurrence that:*

- *results in death*
- *is life-threatening (i.e. with an immediate, not hypothetical, risk of death at the time of the event),*
- *requires hospitalisation or prolongs existing hospitalisation*
- *results in persistent or significant disability or incapacity,*
- *is a congenital anomaly or birth defect (i.e. the outcome of pregnancy involving the patient)*
- *any other important medical condition which, though not included in the above, may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed (e.g. allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias which do not result in hospitalisation, or development of drug dependency).*

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Hospitalisations include planned admissions for elective surgery.

All serious adverse events must be reported on the **serious adverse event form**. The SAE form should be faxed to the AR UK Epidemiology Unit at the University of Manchester on **0161 275 5043 within 7 days** of knowledge of the event. The local principal investigator or research nurse will be contacted by the trials unit if further information is required.

9.3 Adverse Events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram).

Adverse events (either serious or non-serious) which lead to discontinuation of study treatment should be routinely recorded on the CRF. Other adverse events need not be recorded in the CRF.

In addition, new significant muscle symptoms should be sought at each study visit and recorded. If present AND if ALT is greater than the upper limit of normal then a blood CK should be measured (see section 6.2.3)

9.4 Serious Adverse Reactions (SAR)

SERIOUS (as defined in Section 9.2) adverse events, judged by the reporting investigator as having a reasonable causal relationship to atorvastatin, qualify as **serious adverse reactions**. This judgement of causality should be made without breaking the randomisation code – on the assumption that the patient has been exposed to atorvastatin.

SARs should be reported on the **serious adverse event report form** and faxed to the AR UK Epidemiology Unit **within 24 hours** of knowledge of the event.

9.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)

For any reported SAR, the assessment of 'expectedness' will be made by the Chief Investigator (or their delegated deputy) based on the current Summary of Product Characteristics (SmPC)/Package Insert for atorvastatin. If confirmed as a SUSAR will be subject to expedited reporting by the trial sponsor (i.e. Chief Investigator and University of Manchester) to MHRA, therefore every effort should be made to notify the regional trials office within the timeframe shown below (Section 9.7). As a general rule, the treatment code for the specific patient should be broken before reporting a SUSAR to MHRA. Events associated with placebo will usually not satisfy the criteria for a SUSAR.

9.6 Reporting of SAEs, SARs and SUSARs to Pfizer

Although this is an investigator led clinical trial in which Pfizer (the Market Authorisation Holder for atorvastatin) is not acting as sponsor, there is a regulatory requirement that Pfizer be notified of all SAEs, SARs and SUSARs in a timely fashion. This reporting will be carried out by the co-ordinating centre at the University of Manchester and will be separately financed by Pfizer.

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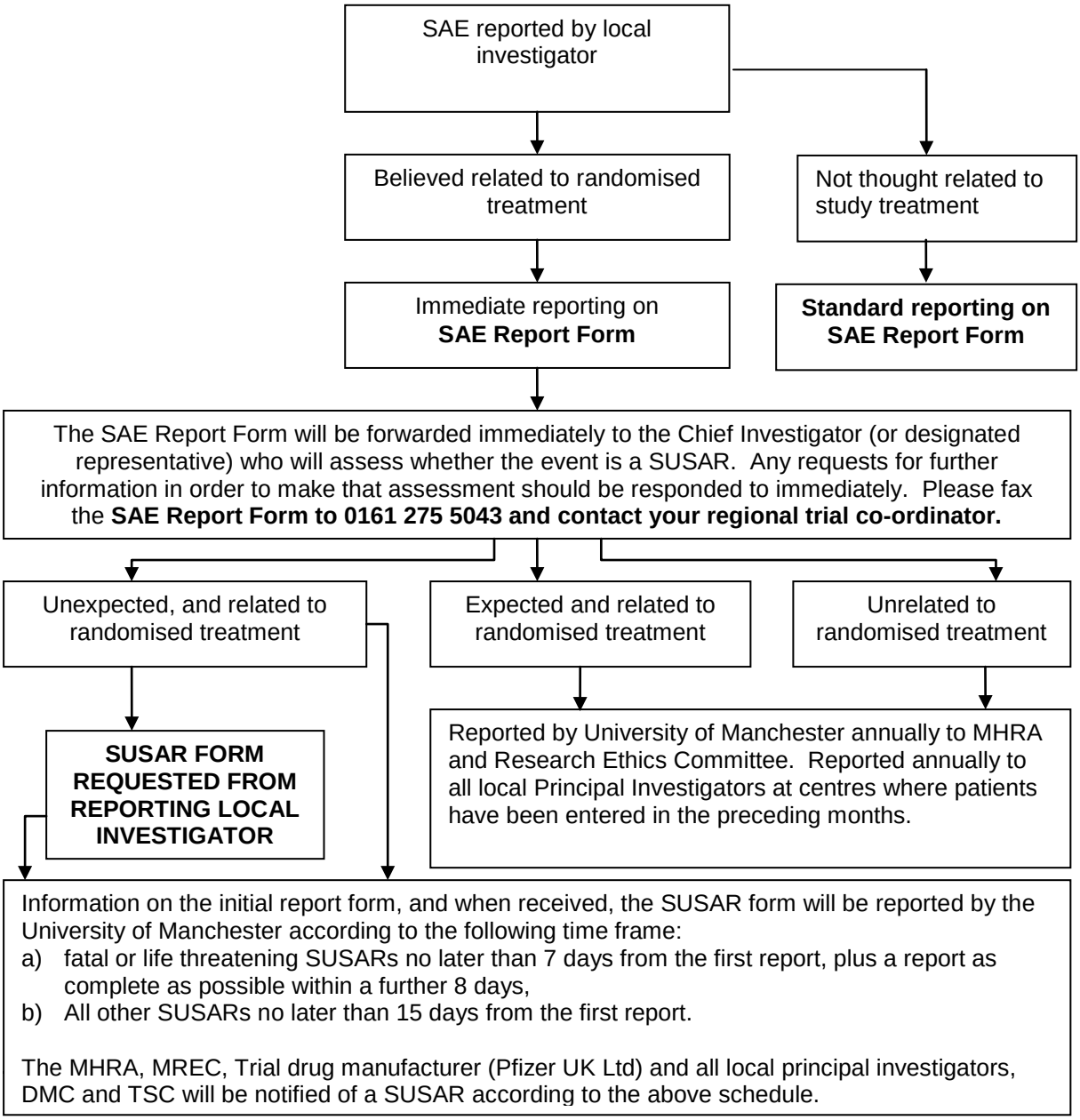
9.7 Recording and reporting of all SAE/SARs

Flow diagram of SAE reporting and action taken following the report:



The patient should be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised. Information on final diagnosis and outcome of SAEs which may not be available at the time the SAE is initially reported should be forwarded on a copy of the SAE initial report form as soon as this information is available. Follow-up may continue after completion of protocol treatment if necessary.

All information regarding an SAE should be faxed to the University of Manchester on **0161 275 5043**, and information required by the drug manufacturer will be passed on by that trials unit. Centres are free to volunteer information to the drug manufacturer if they wish, but are under no obligation to do so.

10. STATISTICAL CONSIDERATIONS

10.1 Sample size

The aim of the trial is to detect (with 80% power at the 5% significance level) a 32% relative risk reduction (RRR) in the primary endpoint attributable to treatment with atorvastatin and anticipating an average of 25% non-compliance. If the ***true*** effect of taking the treatment is a 32% RRR but only 75% of patients are compliant, then ***the effect seen in this trial*** should be about 24% (ie, 75% of 32%). The required number of first events (i.e. patients with events) to be able to detect such a reduction with 80% power at the 5% significance level is 434 (Appendix 8). The estimated ***average blinded event rate in all patients*** is expected to be 1.6-1.8% per annum. A maximum of around 27000 patient-years of follow-up is required for these event rates to produce the required number of first events (Appendix 8). Based on recruitment rates achieved between August 2007 and November 2010 and using a logarithmic decay model to reflect the decline in recruitment with time, it is estimated that 5342 patients recruited by March 2014 would provide between 27000 and 28000 patient-years of follow-up. If the blinded event rate is somewhat less than expected then the trial will continue (if necessary) until the required number of events has been accrued and all the available follow-up data will be used in the analysis.

10.2 Planned recruitment rate

With the anticipated support of up to 120 centres/sites within the UK, the logarithmic decay model predicts that the required number of patients will be recruited by March 2014 (assuming follow-up until March 2016).

The trial manager and trial co-ordinators will continue to provide support to their respective recruitment centres and the relevant research nurses employed through the CLRN and other mechanisms.

The trial will continue to be publicised through the AR UK's "Arthritis Today" magazine and through the National Rheumatoid Arthritis Society (NRAS) as well as local resources. A British Society for Rheumatology (BSR) special interest group has been set up to act as a forum for the study investigators and TRACE RA news are regularly discussed in the quarterly BSR leaflet. A TRACE RA website has also been established.

10.3 Compliance

Compliance will be estimated based on patient reports on Case Report Forms and patients will be considered compliant if they report taking 'most' of their study tablets since their last visit. In addition, the difference in LDL cholesterol will be measured in a random sample of 400 participants in June 2011 and at intervals during the trial to allow the average difference in LDL to be estimated.

10.4 Planned analyses

All patients randomised will be included in the analysis, irrespective of whether the study drug is continued (ITT analysis). Cox regression models will be developed for time to occurrence of a first cardiovascular event or serious adverse event using treatment allocation as the independent variable.

The models will be adjusted for factors used in the stratification (centre) and for any baseline imbalances. However, the trial is of sufficient size to expect that most potential confounders (e.g. smoking, aspirin, NSAID/Coxib, corticosteroid, anti-TNF usage etc) are likely to be balanced between the groups. Treatment differences will be expressed as hazard ratios with 95% confidence intervals. Two-sided p values of ≤ 0.05 will be considered significant.
Kaplan-Meier Product Limit (PL) estimates of the survival curves with 95% confidence intervals will be calculated.

Analysis of rheumatology outcomes

All patients randomised in the TRACE RA DAS substudy trial will be included in the analysis, irrespective of whether the study drug is continued (intention–to-treat analysis). The dependent variable will be the

dichotomous variable of EULAR response. Any further baseline variables can be incorporated into the model if necessary to adjust for baseline imbalances. Treatment differences will be expressed as odds ratios with 95% confidence intervals. Two-sided p values of ≤ 0.05 will be considered significant.

10.5 Procedure for accounting for missing data

Tests will be conducted to explore whether missing data are missing at random and appropriate procedures then deployed to impute the missing data.

10.6 Planned sub-group analyses

Sub-group analyses will be carried out with respect to: sex; age (≤65 vs. >65 years); RA disease duration; rheumatoid factor status and anti-TNF therapy (if numbers are sufficient). It is recognised that these sub-analyses will have less statistical power than those based on the whole study sample and this will be reported appropriately.

10.7 Interim analyses and its frequency

Interim analyses will be performed when the number of events reaches 25%, 50% and 75% of the total expected events. No formal stopping rule will be set but the DMC will advise the Chairman of the Trial Steering Committee that the trial should be stopped if, in DMC's view, the randomised comparison in the trial has provided both (a) proof beyond reasonable doubt that for all, or for some, types of patients the trial treatment is clearly indicated or clearly contraindicated in terms of a net difference in major morbidity and mortality, and/or (b) evidence that might reasonably be expected to influence the patient management of clinicians aware of the results of any other studies. Safety data will be continuously monitored by the independent DMC.

10.8 Economic analyses

The trial will not address any economic issues directly but, since EQ5D can be used for health utility assessment [75], the results can subsequently be used for economic modelling and cost-effectiveness based on calculation of QALYs gained.

The trial will also monitor the number of hospital admissions and length of stay that occur via information collated from the CRFs.

11. ASSESSMENT OF EFFICACY AND SAFETY

11.1 Assessment of efficacy outcomes

The records of English and Welsh randomised patients' will be electronically tagged for mortality with the Office for National Statistics (ONS) and Scottish patients at the Scottish Office's Information and Statistics Division (ISD) as well as the local hospital Trusts' Medical Information departments. Underlying cause of death will be ascertained from death certificates provided by ONS and ISD (which also supply details of times and causes of all hospital admissions in Scotland) supplemented by information from hospital records, including post-mortem examinations, if performed.

Hospital admissions will be ascertained at each centre by matching the patient details with national NHS Hospital Episode Statistics. In addition, non-fatal events will be ascertained regularly by contact with each patient. If necessary additional information will be sought from household members, GP or hospital departments.

11.2 Assessment of safety

Statin safety-related outcomes, as stated in Appendix 6, will be monitored by the independent DMC. The only 2 recognised adverse effects of atorvastatin are:

- Myopathy (muscle pain or weakness in association with a raised CK>10x ULN); and
- Liver function abnormalities

These will be monitored at each follow-up by reviewing ALT or AST results and asking about new and significant muscle symptoms.

In the presence of new and significant muscle symptoms:

(a) If CK>10xULN, then stop trial medication - not to be restarted.

(b) If ALT/AST<2xULN and CK are <3xULN, trial medication can be continued with clinical follow-up. Further measurements of ALT/AST and CK can be requested if thought to be necessary by managing rheumatologist.

(c) If ALT/AST >2xULN and/or CK between 3-10xULN retest in 1-2 weeks: (c1) if normalisation has occurred to ALT/AST<2xULN and CK<3xULN then act as per option (b) above; (c2) if CK>10xULN stop trial medication; (c3) if ALT/AST>2xULN and CK again between 3-10xULN retest in 1 week: if elevation persists then stop trial medication.

In the absence of any new and significant muscle symptoms:

In general, if abnormalities of LFTs with atorvastatin are to occur, they are more likely to occur within the first 3-6 months of treatment. After that, any DMARD or non-steroidal therapy (or other medications) would be a more likely cause of LFT abnormalities and the managing rheumatologists should consider stopping these drugs prior to stopping the trial medication. Attribution of LFT abnormalities to the trial medication or anti-rheumatic drug is left to the managing rheumatologist, but the TRACE RA team, including the Chief and Lead Investigators or delegated person could advise, if necessary.

If LFT abnormalities are thought to be attributable to anti-rheumatic medication rather than trial drug: then follow usual rheumatology practice guidelines (e.g. BSR monitoring guidelines).

If LFT abnormalities are thought to be attributable to trial drug rather than other reasons:

(a) If ALT/AST within normal range or <2xULN, then continue trial medication and arrange next follow-up.

(b) If ALT/AST between 2-3xULN then continue trial medication and retest in 1 week. (b1) if normalisation to <2xULN has occurred, then act as per option (a) above. (b2) if ALT/AST persists at between 2-3xULN or more, then temporarily stop trial medication and act as per option (c) below.

(c) If ALT/AST>3xULN continue trial medication and retest one week later: (c1) if ALT/AST has recovered to <2xULN then continue trial medication and act as per options (a) above; (c2) if ALT/AST between 2-3xULN then retest in 1 week and if ALT/AST persists at between 2-3xULN or more, temporarily stop trial medication and act as per option (c3); (c3) if ALT/AST elevation persists at >3xULN then temporarily stop trial medication and retest in 3 weeks: (c3i) if normalisation has occurred, then act as per options (a) or (b), whichever applies; (c3ii) if abnormality persists at >3xULN then stop trial medication – not to be restarted.

12. RESEARCH GOVERNANCE

12.1 Trial administration and logistics

Dudley Group of Hospitals NHS Foundation Trust and the University of Manchester are co-sponsors of the TRACE RA trial. Sponsorship activities and delegated responsibilities are shared between Dudley Group of Hospitals NHS Foundation Trust, the employer of the Chief Investigator (CI); and the University of Manchester, in accordance with the UK Medicines for Human Use (Clinical Trials) Regulations 2004 and in line with the Research Governance Framework for Health and Social Care, April 2005 2nd Edition, and according to ICH GCP. Both parties agree to allow inspection of sponsors' premises by the competent authorities.

Dudley Group of Hospitals NHS Foundation Trust (DGOH) & Chief Investigator responsibilities:

- Put and keep in place arrangements to adhere to ICH GCP
- Ensure that Investigational Medicinal Products (IMPs) are made available to subjects free of charge
- Take appropriate urgent safety measures
- Ensure that Pharmacovigilance is maintained throughout the duration of the trial – please note that the administration of Pharmacovigilance for the trial has been delegated to the University of Manchester by the Chief Investigator.
- Ensure that PIs conduct the study in accordance with ICH GCP, the DOH Research Governance Framework and laws and statutes that relate to the study and any local requirements as may be specified by their host institution.
- Responsibility for putting and keeping in place arrangements to conduct the study according to Good Clinical Practice, the DOH Research Governance Framework and the laws and statutes that relate to the study
- Responsibility to use all reasonable efforts to ensure that the data collected and reported are accurate, complete and identifiable at source; and that record keeping and data transfer procedures adhere to the Data Protection Act 1998.
- Responsibility for monitoring the study in accordance with the arrangements outlined in the submission to the Sponsor.
- Responsibility to supply documentation and reports as deemed necessary by the Sponsor to fulfil its obligations.
- Responsibility to co-operate with audits or inspections undertaken by the host institution, the Sponsor and regulatory authorities, including the MHRA, as required.
- Responsibility to assist investigations into any alleged research misconduct undertaken by or on behalf of the Sponsor.
- Responsibility to make the necessary provision for archiving essential documents.

AR UK Epidemiology Unit, University of Manchester responsibilities:

Trial Administration Responsibilities:

- Request Clinical Trial Authorisation (CTA) and make any amendments that are required for the authorisation
- Undertake to allow inspection of co-sponsors premises
- Gain appropriate authorisations prior to starting the trial, including authorisation from both the NHS Trust research offices and the University of Manchester, ethical approval.
- Give notice of the following events to the appropriate regulatory bodies:
    - amendments to CTA, make representations and amendments
    - amendments to the protocol

- the termination of the trial
- Maintain a Master File containing essential trial documents and to make the file available for statutory inspections by bodies such as the MHRA

Financial Responsibilities:
- Administer funding and co-ordinate any required legal agreements and investigator statements or agreements.

Responsibilities that have been delegated by DGOH & CI:
- Keep records of all adverse events reported by investigators
- Ensure recording and prompt reporting of suspected unexpected serious adverse reactions (SUSARs) to the Chief Investigator
- Ensure investigators are informed of SUSARs
- Provide an annual list of suspected adverse reactions and a safety report to the relevant authorities and committees.

The following responsibilities are retained by the Chief Investigator, or in his absence, a named deputy(s):

- Prompt decision making as to which serious adverse events are SUSARs, and prompt reporting of that to the University of Manchester for onward reporting to the licensing authority.

The following responsibilities are delegated by the Chief Investigator to the local Principal Investigators at each trial centre:

- Obtain Management (R&D/ Research Governance) approval
- Responsibility for putting and keeping in place arrangements to conduct the study according to Good Clinical Practice, the DH Research Governance Framework and the laws and statutes that relate to the study
- Responsibility to liaise with Pharmacy to document the supply, handling and accountability of all trial drugs
- Responsibility to ensure that all members of the study team have sufficient knowledge, training and experience to undertake the roles assigned to them and to comply with requirements as specified by the host organisation
- Responsibility to maintain a Site File (containing the essential documents) and to make the site file available for inspection if requested by the CI (on behalf of the Sponsors)
- Responsibility to conduct the study in accordance with the agreed research protocol *except where necessary to eliminate (an) immediate hazard(s)* – These circumstances must be reported to the CI who will be responsible for reporting these events on behalf of the sponsor organisations, to the research ethics committee and the MHRA
- Responsibility to use all reasonable efforts to ensure that the data collected and reported are accurate, complete and identifiable at source; and that record keeping and data transfer procedures adhere to the Data Protection Act 1998
- Responsibility to supply documentation and reports as deemed necessary by the Sponsor
- Responsibility to cooperate with audits or inspections undertaken by the host institution, the Sponsors and regulatory authorities, including the MHRA as required.
- Responsibility to assist investigations into any alleged research misconduct undertaken by or on behalf of the Sponsors
- Responsibility to make the necessary local provision for archiving essential documents

The delegation of sponsorship responsibilities does not impact on or alter standard NHS indemnity cover. The agreement of delegated responsibilities is viewed as a partnership and as such it is necessary to share pertinent information between the University of Manchester and the Dudley Group of Hospitals NHS Trust/Chief Investigator, including proposed inspections by the MHRA and/or other regulatory bodies.

12.2 Compliance with Protocol

TRACE RA is being conducted in accordance with the professional and regulatory standards required for non commercial research in the NHS under the UK Medicines for Human Use (Clinical Trials) Regulations

2004. Before activating the trial, participating centres are required to sign an agreement accepting delegated responsibilities for all trial activity which takes place within their centre.

12.3 Good Clinical Practice

This trial will be conducted in accordance with the protocol, the conditions and principles stipulated in the Medicines for Human Use (Clinical Trials) Regulations 2004 and all other applicable regulatory requirements.

12.4 Data acquisition and monitoring

Trials unit staff will visit the participating centres to confirm that agreements are being adhered to, specifically to carry out source data verification and confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki. Copies of the Declaration may be obtained from the designated regional trials unit. By participating in the TRACE RA trial, Principal Investigators at each centre are confirming agreement with his/her local NHS Trust to ensure the following:

- Sufficient data is recorded for all participating patients to enable accurate linkage between patient hospital records and trial case report forms.
- Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits
- All staff at their individual centres who are involved with the trial will meet the requirements of working within the statutory provisions of UK law.
- Original consent forms are dated and signed by both patient and investigator and are kept together in a central log together with a copy of the specific patient information sheet(s) given to the patient at the time of consent. The original consent form must be kept in the centre site file and copies of the consent form should be given to the patient, filed in the patient hospital notes and also forwarded to the regional trials unit.
- Copies of CRFs are retained for 15 years at the NHS Trusts and the University of Manchester to comply with international and organisational regulations
- Staff will comply with the Standard Operating Procedures for TRACE RA

The affiliated trials units will monitor receipt of CRFs, evaluate incoming CRFs for compliance with the protocol and resolve inconsistencies and missing data queries.

Participating centres will be monitored by their allocated trials unit and also possibly by the relevant regulatory authorities. Monitoring by the units will confirm compliance with the protocol and source data verification (SDV). The Trial Manager (based in Manchester) will establish quality assurance proformas to be completed by the trial co-ordinators when visiting the participating NHS Trusts. Some combined visits between the trials units will be conducted to ensure consistency of approach.

The frequency of monitoring will be determined according to a risk assessment model approved by the TSC. If any problems are detected in the course of the monitoring/auditing visits, then the Principal Investigator and the trials unit will work together to resolve queries.

12.5 Data handling and record keeping

All data will be entered on to a computerised database at the trials units. All data will be identified via a unique trial number and data tables will be linked using this number. The names and addresses of patients matched to their trial number will be stored in a separate secure database. All databases will be password protected and stored according to the requirements of the Data Protection Act 1998.

12.6 Archiving

All source and study documentation must be securely retained by the local Principal Investigator for 15 years after the trial has ended. An end of study visit may be performed by the trials units to resolve any data queries and outstanding trial documentation before the documentation can be archived by the participating centre. Source data (including data on any patients who die) must be retained for the

duration of the recruitment, treatment and follow up phases of the trial for inspection by representatives of trials units.

12.7 Financial matters

TRACE RA is investigator-designed and led, and is jointly funded by Arthritis Research UK and the British Heart Foundation. Pfizer UK Limited has provided free active trial drug and placebo for the whole of TRACE RA, as well as an unrestricted educational grant for the TRACE RA-DAS and the TRACE RA BIOBANK sub-studies. If additional financial support is received from any other source, this will be made apparent to the approving MREC but will not require a protocol amendment.

Cost implications to the NHS Trusts:
Support for local set-up costs (£300 per centre), local pharmacy set-up and running costs (£200 per centre) and local research nurse time (£70 per recruited patient) will be made available to collaborating NHS Trusts. Invoicing should be raised by the participating trial centres to their respective trials units. The trials centres will be contacted at the end of trial recruitment to ensure that payment has been received by the centre for the services provided. Additional support in terms of human resources will be provided to the trial centres by the trial units, through the trial co-ordinators (for the duration of the trial) and centrally-appointed trial nurses (for the initial 2 years of the trial), subject to satisfactory honorary contracts and reciprocal agreements.

The trial and its substudies have all been adopted by the UKCRN Clinical Research Network and are therefore eligible for additional support through this funding stream via each Comprehensive Local Research Network (CLRN),

12.8 Ethical considerations

The original trial protocol was submitted for ethical review to COREC. The MREC ref no is 06/Q1704/171. The trial did NOT commence recruitment until central (MREC & MHRA) and individual site (SSI & R&D) regulatory approvals were in place at each recruiting centre. Any subsequent amendments (including this revised protocol) will be submitted to the same MREC and will not be implemented until approval has been received and notified to all participating sites.

The main ethical consideration pertaining to the TRACE RA trial is whether the trial should be terminated early if efficacy of atorvastatin is proven. The planned interim analyses should ensure that the trial continues only as long as is needed to establish, beyond reasonable doubt, that treatment with atorvastatin is either beneficial or harmful to patients with RA.

12.9 Publication Policy

The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The trials units and all participating centres and clinicians will be acknowledged in this publication.

All presentation and publications relating to the trial must be authorised by the TRACE RA Trial Steering Committee.

No investigator may, at any time, present or attempt to publish data relating to the TRACE RA trial and its sub studies without prior permission from the Trial Steering Committee.

13. DISSEMINATION OF RESULTS

13.1 Informing trial participants

Participating centres will be sent a list of their patients along with their allocated treatment arm at the end of the trial. They will then be able to inform those patients who wish to know which treatment arm they were allocated.

13.2 Expected value of the results

The proposed trial will add to the evidence base of how to reduce the cardiovascular risk of patients with RA. It may identify an intervention that will reduce the incidence of the most common cause of death in the most common form of chronic inflammatory arthritis. The trial will also be used to define RA specific CV risk profiles, which can be utilised to identify patients at high risk and inform the need for further investigation and treatment.

Indirectly, this trial may provide some insight into the link between inflammation (in this case, high-grade inflammation) and CVD and provide mechanistic clues that can be investigated specifically in subsequent studies. TRACE RA BioBank will be an excellent resource to address such questions at the basic scientific level.

The TRACE RA-DAS sub-study will add to the evidence base of compounds which have disease modifying properties in RA. If benefit is shown, it is likely that atorvastatin might then be used in combination with other DMARDs to improve overall disease control. This information would be of most benefit in patients with a known high CVD risk.

14. CONFIDENTIALITY AND LIABILITY

14.1 Confidentiality

The trials units (Dudley, Dundee & Manchester) will comply with all aspects of the Data Protection Act 1998. All information collected during the course of the trial will be kept strictly confidential.

Patients NHS numbers will be collected on a patient eligibility and registration form (this will be returned to Manchester Trials Unit) at the beginning of the trial. All other data collection forms, which are faxed/posted to the trials unit, will be coded with 3 patient identifiers (Patient's Initials, Centre numbers and Patient Identification Number). Information will be held securely on paper and electronically at the trials units, including appropriate storage, restricted access and disposal arrangements of patients' personal and clinical details. Participants will also not be identified in the results of the study.

Patient information recorded in their medical records will be accessed during identification of potential patients and when site monitoring visits occur to ensure that the trial is being carried out according to ICH GCP guidelines.

Stored patient information will be kept on NHS and University computers so as to be able to track the number of patients on the trial. Data from patients' medical records will be transcribed onto case report forms.

All clinical information about patients will be stored on a central database at the University of Manchester. The main database and any sub-databases will be password protected and stored according to the requirements of the Data Protection Act 1998.

On occasion, if quality of life questionnaires are not completed in clinics due to time constraints or patients not attending clinic, the questionnaire may be posted by the research nurse for patients to complete and return to the University of Manchester Trials Unit (a SAE will be provided to facilitate this).

The local principal investigators must keep a separate log of patients' trial numbers, names, addresses and hospital numbers. The local principal investigator must maintain in strict confidence trial documents, which are to be held in the local hospital (e.g. patients' written informed consent forms). The local principal investigator must also ensure that patient confidentiality is maintained.

The trials units will maintain confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, other than reporting of serious adverse events. Representatives of the trials units will be required to have access to patients medical records for quality assurance purposes but patients should be assured that their confidentiality will be respected at all times. This will be stated in the patient information sheet.

14.2 Liability/ Indemnity/ Insurance

The individual NHS trusts have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial and the NHS trusts remain liable for clinical negligence and other negligent harm to patients under this duty of care. Indemnity for participating hospitals is provided by the usual NHS indemnity agreements.

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APPENDIX 1: Sub Study 1:
TRACE RA DAS (DISEASE ACTIVITY SUB-STUDY)

A1.1 Study Hypothesis

- Atorvastatin is more effective than placebo as adjuvant therapy for the control of disease activity in patients with RA
- Atorvastatin is more effective than placebo as adjuvant therapy in slowing radiographic damage and the long-term decline in physical function in patients with RA
- RNA samples will allow gene expression profiling studies in RA. Blood samples collected from this patient population would facilitate research in a broader array gene expression profiling approach and would allow assessment of differential expression of genes without *a priori* information.

A1.2 Study Design

A multicentre, randomised, double blind, placebo-controlled trial of atorvastatin 40mg once daily for control of disease activity in patients with RA aged ≥50 years or with ≥10 years of RA disease duration (if under 50 years of age). This is a sub-study of the main TRACE RA trial which explores the influence of atorvastatin on cardiovascular endpoints.

A total of ***326 patients*** will be required and each patient will be followed for two years (with respect to the sub-study but will also be followed up until the end of the cardiovascular/main study).

The inclusion and exclusion criteria for the disease activity sub-study are similar to the main study with the express ***proviso that all patients entering the sub-study must have a baseline DAS28 score of ≥3.2***.

A1.3 Proposed Duration of Treatment, Follow up and Frequency of Intervention

Patients participating in this substudy will have an additional nurse global assessment and be asked to provide a blood sample for mRNA, serum and plasma extraction at baseline and month 6 of their trial visit. (As outlined in Appendix 2)

Patients will also have the following assessment in Months 6, 12, and 24:
28 tender and swollen joint counts
Patient global assessment
Nurse global assessment
ESR and/or CRP

A1.4 Proposed Sample Size

A sample size of 326 patients is required to provide 80% power at the 5% significance rate to detect a difference in EULAR response rate between statin treated and the placebo arms. This assumes a 20% response rate in the placebo arm and 20% loss to follow-up during the 2 years of the sub-study.

A1.5 Planned Analysis

All patients randomised in the trial will be included in the analysis, irrespective of whether the study drug was discontinued (ITT analysis). EULAR response rates in the two arms will be compared using odds ratios with 95% confidence intervals and adjusting for any baseline differences between the groups. Rheumatology efficacy outcomes will be recorded at 6, 12 and 24 months visits. For safety outcomes, logistic regression models will be used for analysis with treatment allocation together with the factors used for stratification. Any further baseline variables can be incorporated into the model if necessary to adjust for baseline imbalances. Two-sided p values of ≤0.05 will be considered significant.

A1.6 Planned Sub-group Analysis

Sub-group analyses will be carried out with respect to: gender, age group (≤65 vs. >65 years), RA disease duration, rheumatoid factor status and anti TNF therapy (if number is sufficient).

A1.7 Proposed Frequency of Analysis

No interim analysis is planned for TRACE RA DAS. Safety data will be continuously monitored by the independent DMC.

A1.8 Proposed Collection and Use of blood samples

A repository committee will be created by the Trial Steering Committee (TSC) to oversee work relating to the blood samples and to consider requests from other academic and clinical research organisations for the blood samples. All requests from academic or pharmaceutical organisations to use the samples would be submitted to an ethics committee for regulatory approval.

APPENDIX 2: Sub Study 2:
TRACE RA BioBank (A Molecular biomarker and genetic sub study)

A2.1 Background

Rheumatoid Arthritis (RA) was previously considered to be a benign, controllable disease with a reasonably good prognosis in the majority of patients. It is now known that it can be a severe, progressive disorder associated with a premature mortality. Patients with RA have a 5-year mortality rate similar to that of patients post myocardial infarction (MI), with triple coronary vessel disease or with neoplastic disease, RA should be viewed as an urgent medical problem requiring immediate intervention. Despite this, research targeted to cardiovascular disease (CVD), the main cause of death in RA, was ignored for many years. In RA life span is shortened by approximately 15-20% from the date of onset of the illness.

Between 34-40% of the excess deaths are from cardiovascular causes. Various studies have given Standard Mortality Ratios for CVD in RA of between 1.51 to 5.25, where the lower estimate is for MI only and the largest includes heart failure. The TRACE RA study addresses the clinical problem of enhanced CV mortality in this group of patients via a randomised controlled trial (RCT) of Atorvastatin versus placebo in 3,808 RA patients. This study is funded by the arc and the British Heart Foundation and will provide novel data on the beneficial, or otherwise, effects of a statin on CV events and mortality in RA. The aim of the trial is to establish whether atorvastatin will protect patients with RA aged ≥50 years or with ≥10 years' duration of RA from fatal and non-fatal atherosclerotic events. 3,808 subjects are to be recruited from 60 centres over 18m, and undergo treatment with atorvastatin or placebo for 5 years after recruitment of the last patient. CV events and mortality is the primary endpoint. A nested sub-study *(TRACE RA-DAS)* has also been designed to determine whether atorvastatin, used in conjunction with standard DMARD therapy, will provide added arthritis control in patients with moderately or severely active RA. TRACE RA-DAS will recruit 326 patients and will run for 2 years. The primary endpoint is EULAR 'moderate' or 'good' response using the DAS 28.

However, such a trial, where the study population is large and well characterised, also provides unique opportunities for major studies, particularly those where DNA/RNA and biomarkers can be used to shed light on disease susceptibility, outcome and drug responsiveness. Familial, twin, admixture and migration studies all indicate a substantial contribution of genetic factors in the aetiology of this common complex disorder. Substantial advances in gene identification are now being made: linkage scans have highlighted consistently replicated regions harbouring susceptibility genes and a growing number of substantiated susceptibility variants have been defined. Further progress in definition and characterisation of novel genes will require a large community-based RA DNA resource, enriched by the availability of detailed long-term clinical follow-up.

This resource will allow: study of the modest relative risks expected of many susceptibility variants (by comparison with 'normal' populations), replication of other resources, measurement of the population attributable risk of susceptibility variants, evaluation of potential gene/gene and gene/environment interactions, definition of complication-related susceptibility variants, and exploration of genetic effects on treatment response. There is, therefore, a clear case to be made for establishing such a resource on the basis of genetic studies alone.

In addition the study of inflammation and CV disorders is evolving, in particular biomarkers for disease progression and events are becoming available, and more will be uncovered. A resource of banked serum and plasma from a well-phenotyped large population has the potential to answer questions relating to these novel mechanisms in a rapid, powered and convincing fashion. These resources will also provide a substrate for the 'omic' disciplines. Mircroarray analysis of the transcriptome is now a mature field and continues to provide insight into prognosis in many disease areas, and is likely to be highly informative in the study of drug response in clinical trials. The collection of plasma and serum ion the proposed Biobank will also provide a substrate for the emerging proteomic and metabonomic studies.

A2.2 Study Aims

- To develop a DNA repository for consenting patients with rheumatoid arthritis (RA) enrolled in the TRACE RA study, in centres that agree to provide such samples.

- To develop an RNA repository for gene expression profiling from consenting patients in the TRACE RA-DAS substudy at 2 time points (baseline and 6months).
- To develop a plasma and serum repository for the above patients from centres where such blood preparation is possible, and the centres agree to provide such samples.
- To devise and complete peer-reviewed projects on the above samples using the phenotypic and outcome data collected in the TRACE RA trial.
- To take advantage of established population-based record-linkage capability, to allow longitudinal tracking of the subjects, thereby enabling investigation of the relationship between susceptibility genotypes and pertinent clinical features including characteristics at diagnosis, response to treatment, development of RA complications, vascular disease and survival.

To develop an infrastructure surrounding the collection, storage and use of these samples which concerns itself with ethics, consent, privacy and collaboration, to protect the rights of the patients whilst maintaining the highest standards of clinical research

A2.3 Methodology:

Informed consent and blood will be collected from 5,350 patients with RA that are participating in the main TRACE RA study.

a. Subjects:

The subjects will be those enrolled into the TRACE RA study (inclusion and exclusion criteria described in TRACE RA protocol). More than 4000 RA patients will be enrolled in up to 120 centres. The RNA (see below) will be sampled from the 326 subjects in the TRACE RA-DAS substudy, who give consent for this sampling. As it may not be possible to collect serum and plasma from all centres due to centrifuge and freezer availability, only DNA samples may be collected from all TRACE RA trial participants, with as many as possible of these giving also plasma and serum. Although this protocol defines a 3,808 population this caveat applies throughout.

b. Sample handling and DNA extraction:

The following blood samples will be taken from each subject who gives consent. DNA will be collected from all consenting subjects, and serum and plasma where possible from as many subjects as can be managed: One 4.5mls citrate sample (for plasma), two 10mls EDTA (for plasma), two 10mls clotted (for serum), two 10mls EDTA (for DNA, immediately stored, without spinning, at –20/-80C OR sent on ice within 48hrs). The same samples will be taken from patients in the DAS substudy at baseline, with the addition of 4 x 2.5 mls samples for RNA sampling. Serum and plasma (same volumes as above) and RNA will also be taken at 6months from patients in the TRACE RA-DAS substudy who have given consent for sampling. Serum and plasma will be prepared, aliquoted and frozen at the collection site in an appropriately timely fashion where possible, as this is optimum for sample preparation and costs. Where whole blood is to be stored the Biobank co-ordinator will work with the centre to obtain ratification of temporary sample storage at the centre under the Tissue Act. Those samples which are frozen will be transported in batches on dry ice via Courier in specially prepared packages routinely used by the group for sample transfer. Transfer to Ninewells Hospital will be followed by appropriate further sample preparation, and storage in alarmed secure freezers. DNA will be prepared from 10mls of blood using Promega Wizard blood DNA preparation procedure (with one sample remaining as back up) and all samples will be quantified by fluorescence dye techniques to maximise standardisation of concentrations, an essential prerequisite to robust, quality high throughput genotyping. Finally, each sample will be tested in a multiplex PCR reaction that will include an SRY marker (a Y-specific amplicon, as a check on identity integrity) and one autosomal marker (such as beta-actin) (to confirm DNA quality). DNA quantification, normalisation, dilution and aliquoting will be performed using an Xiril X100 liquid handling robot (available in Dundee), and stored at -30^0c in bar coded replicate 96 and 384 well plates. Importantly, DNA samples will be bar-coded and the robot will confirm the identity of each sample and track the progress of each sample to all daughter plates. Normalized DNA will be distributed to Pfizer and to Manchester in 96 well format.

c. RNA extraction: Whole blood samples will be taken in four 2.5mls PAXgene RNA stabilization vacutainers (BD/Qiagen) from each of the 326 subjects in the TRACE RA-DAS substudy on two occasions ie time zero and at 6m, to correlate with clinical disease activity measures. RNA will be prepared in a 96

well format using QiAMP PAXgene 96 blood RNA system. This will be run as a semi-automated process using a Xiril X100 liquid handling robot. RNA will be assessed for integrity by lab-on-a-chip technology using an Agilent 2100 Bioanalyzer.

A2.4 Projects and Statistics:

A Repository Committee will be set up to oversee the work relating to these samples, and to consider requests from other centres for DNA. This committee will consist of the Chief and Lead Investigators, the AR UK selected Trial Steering Committee chairman (Prof Gordon Lowe, University of Glasgow), amongst others, including patient representation. The potential for study of these samples is huge and 3 exemplar projects have been appended. These are merely examples of many possible projects which will be developed by the Repository Steering Committee, in collaboration with others. All requests from academic or pharmaceutical organisations to use the samples would be submitted to an ethics committee for regulatory approval.

The mainstay of analyses based on this resource will be using conventional genetic/serum/plasma statistical methodology, encompassing a range of different analytical approaches and study objectives (including for example, single-locus and haplotype-based studies; biological and positional candidate analyses; replication studies for associations uncovered in other (smaller) populations; logistic regression analyses seeking to dissect LD structure and define aetiological variants; and gene-gene interactions). In addition, the associated longitudinal clinical data will permit analyses of the relationship between genotypes of interest and pertinent outcomes including complication rates; treatment response; survival/mortality; and disease progression. These data will be analysed using multivariate regression and Cox regression methods, including algorithms for repeated measures when appropriate. The trial statistician is Dr Peter Nightingale, (University of Birmingham, The Wellcome Trust Clinical Research Facility), who has ensured the appropriate powering of TRACE RA, and who is involved in the day to day statistical issues of the Trial.

The mainstay of analyses based on this resource will be using conventional genetic/serum/plasma statistical methodology, encompassing a range of different analytical approaches and study objectives (including for example, single-locus and haplotype-based studies; biological and positional candidate analyses; replication studies for associations uncovered in other (smaller) populations; logistic regression analyses seeking to dissect LD structure and define aetiological variants; and gene-gene interactions). In addition, the associated longitudinal clinical data will permit analyses of the relationship between genotypes of interest and pertinent outcomes including complication rates; treatment response; survival/mortality; and disease progression. These data will be analysed using multivariate regression and Cox regression methods, including algorithms for repeated measures when appropriate.

A2.5 Facilities and Experience available for the study:

Dundee's Ninewells Hospital is uniquely placed to act as the physical Repository; due to its experience in such studies to date. Dr Colin Palmer and Professor Jill Belch have extensive experience in sample preparation for these types of studies.

These include grants from TENOVUS to pilot endothelial studies in a large population of patients with diabetes, the Raynaud's and Scleroderma Association to link the development of carotid vascular disease to certain genotypes in Systemic sclerosis, from the Wellcome Trust UK Case/control study of type 2 diabetes, where all subjects (n=15000) are from Tayside. Tayside is also the principal centre for the recruitment and sample handling for Generation Scotland, with 10,000 individuals to be targeted within the next 2 years, growing to 50,000 Scotland wide by the end of 2011. The robotics and software developed for these large studies will easily accommodate the currently proposed sample throughput.

POPADAD, a Scotland wide 8 year CV mortality trial (n= 1,320) also has Ninewells (and the Dundee applicants) as its core laboratory for sample collection. In addition we have recently developed a "High Volume" genotyping workflow to complement our "high throughput" affymetrix and Illumina systems, where we can cheaply and efficiently genotype 10,000 patient samples for 1 SNP in 2 hours. This system uses both KASPAR indirect allelic discrimination and TAQMAN based allelic discrimination. KASPAR is simpler and much cheaper, but assays that fail on KASPAR will be performed on TAQMAN. Both genotyping techniques are homogenous fluorescent assays that can be performed easily in an automated fashion. Sample reformatting will be performed to 384 well formats on a Xiril liquid handling robot. Reaction

mixtures will be dispensed to 384 using a DEERAC high speed nanodispenser (1-2ul total reaction volumes). PCR will be performed in a H2OBIT ultra-high-throughput thermal cycler (10,000 samples per 2 hour run) and the final genotypes scored using an Applied Biosystem SDS9700. The genotyping project will be analysed, managed and quality controlled using a dedicated genotyping database system (KLUSTERCALLER, KBiosciences).

Standard analytical techniques, in addition to genetic studies, include HPLC-MS, GC-MSMS, ELISA, Spectrophotometry, Affymetrix micro-array, MALDI, proteomics (Prof Mike Ferguson), flow cytometry, (Luminex Bead array) and Western Blotting.

A2.6 Ethical considerations

a. Confidentiality, security, ethics and database management

With the implementation of the new data protection act issues of data security and confidentiality are very much in the public eye, as they should be. The mechanisms employed to ensure appropriate security and confidentiality within Ninewells result from years of deliberation and debate and are continually reviewed and updated in parallel with legal and ethical requirements. The exemplar project for Ninewells is the DARTS project, (Diabetes Audit and Research Tayside). As an example of how TRACE RA samples will be treated using DARTS logistics will be explained below.

Clinical information on DARTS is stored on a Structured Query Language (SQL) database. Clinical information is accessed via a Web server and Web browser. The first level of security on clinical data is that imposed by the NHS-NET network. Although DARTS has a presence on the wider Internet, users from the Internet cannot access the DARTS Web Server located within the confines of NHS-NET. A login screen is presented and communications are all encrypted, and access determined by username and password. All attempts to log-on to DARTS and every action subsequently taken are logged producing audit trails. For DARTS anonymous Genetic research we use all the security and confidentiality mechanisms provided by the Microsoft SQL Server V7 platform.

The Tenovus grant award has allowed us to implement a secure system for anonymous genetic case/control studies. Every patient, GP, general practice and hospital clinic represented on the system is allocated a unique randomly generated identifier intended for the purposes of anonymous research. Researchers are then restricted to ‘views’ of data that use these anonymous identifiers and omit any identifying fields.

Thus, all demographic information is removed except sex, age (in months), and social class (Carstair’s Index). For genetic research, only the nurse performing the fieldwork has access to the patients identifying numbers. This nurse does not have access to any other patient-specific data. In addition, although the system administrator (through necessity) has access to all data on the server, the identity of individual genetic markers is not available to him.

The present information sheet is included in Appendix 3. It has been modified according to MRC guidelines to state that products derived from the sample may be used by other researchers and the commercial sector. It includes specific clauses that allow use of samples for RA and wider medical issues including drug response.

All record linkage studies and issues relating to confidentiality, anonymisation of data and dataset security will come under the aegis of the Health Informatics Centre at the University of Dundee. This has an external scientific Advisory Board (chair Professor Elizabeth Russell, Professor of Epidemiology, University of Aberdeen) that scrutinises all anonymised record linkage research in Tayside according to published standard operating procedures.

b. Administration of the Collection

To maximise the utility of the proposed DNA resource, the collection will be overseen, and access to the resource managed, by the TRACE RA Repository Committee. This steering group would become the custodian of the DNA resource to ensure that maximum benefit is derived from the collection whilst avoiding any unnecessary duplication of genotyping/assaying.

DNA aliquots will be made and master stocks stored in Dundee. Complete plated collections of the DNA (~15ug) will be distributed to the appropriate collaborating centres (see exemplars below ie Manchester). Requests for DNA from external collaborators will be considered. Written applications will be to test specific variants within a gene and standardized data will be required in these requests: data to establish the importance of the gene, the role of the specific variants to be typed eg coding variants, haplotype tagging SNPs etc, details of the assay used for SNPs, preliminary data to give allele frequencies and power calculation.
Permission will be given to exclusively (for one year after permission is granted) test the requested specific SNPS. DNA aliquots may be obtained from Dundee DNA will be given blinded and will include approximately 10% of samples with the most DNA as duplicates to provide a measure of genotyping accuracy. A condition of using the resource will be that all genotyping will be given to the core database so that these data are held centrally; the specific data field however will remain under the custodianship of the scientist performing the study until the data are published. The analysis of the ongoing longitudinal data will be obtained by users of the resource working with the epidemiological team in Dundee. A collaborative framework has been established in the recent SRIF-funded Health Informatics Centre at Ninewells Hospital.
The Health Informatics Centre thus has standard operating procedures that facilitate this collaborative inter-institutional research on anonymised datasets for approved projects. In order to ensure the continuation and the development of this resource, a cost recovery charge will be levied for the supply of DNA and subsequent data analysis to external centres from Dundee/Manchester. Pricing will be determined by the Repository committee based on cost recovery and will be aligned with other UK resources. We would use these funds to support the maintenance and development of the resource at Ninewells beyond the period of this award.
Note: the plasma and serum will be utilised by the TRACE RA Steering Committee as this is a more finite resource.

A2.7 Conclusion

We anticipate great demand both nationally and internationally because, to our knowledge there is no comparable publicly available resource.
It will be especially unique because of the longitudinal follow-up of phenotypic data. This Repository will form the basis of an RA Framingham and provide insight into disease mechanisms, complications and drug responsiveness for many years to come.

APPENDIX 3: SAMPLE PATIENT INFORMATION SHEET, CONSENT FORMS AND GP LETTERS

These are provided as separate documents and will be stored in the master trial file, regional trial unit site files and the centres' site files.

Please see list of documents as follows (All documents will be approved by MREC):

1. Patient Information Leaflet - Main TRACE RA trial
2. Patient Information Leaflet - TRACE RA BioBank (Genetic sub-study)
3. Patient Information Leaflet & Consent – TRACE RA DAS and DAS Biobank (Disease Activity sub-study)
4. Consent form Main TRACE RA trial and TRACE RA Biobank (Genetic Substudy)
5. Patient Information Leaflet and Consent - DNA Collection Only
6. GP letter - for centres that routinely assess RA patients for 10 year cardiovascular disease risk
7. GP letter – for centres that do not routinely assess RA patients for 10 year cardiovascular disease risk
8. GP referral letter
9. Promotional Leaflet – TRACE RA information to patients
10. Promotional Leaflet – TRACE RA information to investigators

APPENDIX 4: QUESTIONNAIRES

These are provided as separate documents and will be stored in the master trial file, regional trial unit site files and the centres' site files.

Please see list of documents as follows (All documents will be approved by MREC):

1. Lifestyle questionnaire
2. Health Assessment Questionnaire (HAQ)
3. EQ5D – EuroQol 5 dimensional lifestyle questionnaire
4. Patient Global Assessment (Visual Analogue Score)
5. Nurse Global Assessment (Visual Analogue Score) - (TRACE RA DAS Substudy only)

APPENDIX 5: DEFINITIONS OF CARDIOVASCULAR ENDPOINTS

An independent cardiovascular endpoint classification committee will review cardiovascular events and all deaths and will classify them according to the WHO MONICA method, or alternative of their choice.

Primary Endpoints

Cardiovascular death (excluding definite haemorrhagic stroke (ICD 10: I62-67; and non-coronary cardiac death (I00- etc), non-fatal myocardial infarction, non-fatal stroke or any coronary or non-coronary revascularisation[77]. This will comprise the following, as defined in the subsequent paragraphs:

Coronary heart disease death
Fatal presumed ischaemic stroke
Other atherosclerotic vascular death
Myocardial infarction
Myocardial infarction
Nonfatal stroke
Transient ischaemic attack -a mild cerebrovascular stroke with reversible symptoms that last from a few minutes to several hours
Coronary revascularization
Non-coronary revascularization (see below for definitions)

Secondary endpoints

Cause-specific mortality (coronary, other vascular and non-vascular death separately)

A5.1 FATAL ENDPOINTS

A5.1.1 Coronary heart disease death

Death certificate or equivalent documentation with consistent or underlying or immediate cause plus one of the following:

i. Preterminal hospitalisation with acute myocardial infarction (see definitions below).
ii. Previous documented angina or myocardial infarction when no other cause other than atherosclerotic coronary heart disease death could be ascribed as the cause of death.
iii. Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms of myocardial ischaemia, and accompanied by presumed new ST segment elevation, or new LBBB, and/or evidence of fresh coronary artery thrombosis by coronary arteriography, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
iv. Autopsy evidence of acute coronary arterial thrombosis and/or acute myocardial infarction.

A5.1.2 Suspect coronary heart disease death

Death certificate or equivalent documentation with consistent underlying or immediate cause but neither adequate preterminal documentation of the event nor previous diagnosis of atherosclerotic coronary heart disease.

A5.1.3 Fatal Presumed ischaemic Stroke

Death certificate or equivalent documentation with consistent or underlying or immediate cause plus either:

i. Preterminal diagnosis of stroke (see definitions below).
ii. Autopsy evidence of cerebral infarction

A5.1.5 Other atherosclerotic cardiovascular death (e.g. ruptured aortic aneurysm, mesenteric infarction, peripheral arterial disease):

Death certificate or equivalent documentation with consistent underlying or immediate cause and adequate preterminal documentation of the event.

Note: Preterminal documentation and/or information may include hospitalisation for, or diagnosis of, a vascular-related illness for a previous event other than the terminal event.

A5.1.6 Non-cardiovascular death:

Death certificate or equivalent documentation with diagnosis consistent with preterminal documentation and/or information.
Death certificate only

Note: When no formal written documentation is available, verbal information from relative and/or witness will be admissible and should be recorded on the appropriate study forms.

A5.2 NON-FATAL EVENTS

A5.2.1 Acute myocardial infarction (Universal definition of myocardial infarction, Thygesen et al Eur Heart J 2007;28:2525-8)

Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:

Symptoms of ischaemia
ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)] (see glossary)
Development of pathological Q waves in the ECG (see glossary)
Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Elevations of troponin for other causes, in the absence of evidence of myocardial ischaemia, will not be classified as myocardial infarction (see glossary).

For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3x99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognised.

For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5x99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.

A5.2.3 Coronary Revascularisation

Coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (angioplasty, atherectomy, laser ablation or stenting or any newly introduced invasive method for the management of coronary artery disease).
Note: Acceptable documentation will include hospital discharge letters, operation notes or other clinical correspondence documenting performance & date of procedure.

A5.2.4 Stroke (any event that meets the criteria listed below for one of the following 3 categories of stroke):

Ischaemic stroke (one of the following conditions must be met):
Rapid onset of focal neurological deficit lasting ≥24 hours or leading to death plus evidence from neuroimaging (CT or MRI) showing cerebral/cerebellar infarction or no abnormality, or post-mortem examination showing cerebral and/or cerebellar infarction.
Rapid onset of global neurologic deficit (e.g. coma) lasting ≥24 hours or leading to death plus evidence from neuroimaging showing cerebral/cerebellar infarction, or post-mortem examination showing infarction.
Focal neurologic deficit (mode of onset uncertain) lasting ≥24 hours or leading to death plus evidence from neuroimaging showing cerebral/cerebellar infarction, or post-mortem examination showing infarction.

Primary intercerebral and/or cerebellar haemorrhage (one of the following conditions must be met):
Rapid onset of focal neurologic deficit lasting ≥24 hours or leading to death plus evidence from neuroimaging or post-mortem examination showing primary intracerebral and/or cerebellar haemorrhage.
Rapid onset of global neurologic deficit (e.g. coma) lasting ≥24 hours or leading to death, plus evidence from neuroimaging or post-mortem examination showing primary intracerebral and cerebellar haemorrhage.
Focal neurologic deficit (mode of onset uncertain) lasting ≥24 hours or leading to death, plus evidence from neuroimaging or post-mortem examination showing primary intracerebral and/or cerebellar haemorrhage.

Stroke- mechanism unknown (one of the following conditions must be met):
Rapid onset of focal neurologic deficit lasting ≥24 hours or leading to death, without neuroimaging or post-mortem data available.
Rapid onset of global neurologic deficit (e.g. coma) lasting ≥24 hours or leading to death, without neuroimaging or post-mortem data available.
Focal neurologic deficit (mode of onset uncertain) lasting ≥24 hours or leading to death, without neuroimaging or post-mortem data available.

Note: The following **conditions will be excluded** from the defined endpoint of stroke as outlined above:
Primary intracerebral haemorrhage
Primary subarachnoid haemorrhage
Subdural or extradural haematoma
Traumatic intracerebral haemorrhage
Neurologic deficit due to major metabolic or haemodynamic disturbance
Venous sinus thrombosis
Cerebral tumour
Cerebral embolism secondary to infective endocarditis
Any other causes of neurological deficit which, in the opinion of the committee, are not primarily cardiovascular in origin

A5.2.5 Carotid revascularisation

Coronary endarterectomy or percutaneous carotid intervention (angioplasty, atherectomy, laser ablation or stenting or any newly introduced invasive method for the management of carotid artery disease).
Note: Acceptable documentation will include hospital discharge letters, operation notes or other clinical correspondence documenting performance of procedure & date.

A5.2.6 Non-fatal peripheral atherosclerotic events

Hospital-verified acute peripheral arterial ischaemic events. The diagnosis is based on symptoms, clinical findings and/or appropriate radiological investigations.

A5.2.7 Peripheral arterial revascularisation

Any one of :
Repair of aneurysm or peripheral arterial revascularisation by open surgical or percutaneous techniques (angioplasty, atherectomy, laser ablation or stenting or any newly introduced invasive method for the management of aortic or peripheral arterial disease).
Above-ankle amputation for critical limb ischaemia
Chemical or surgical sympathectomy for atherosclerotic peripheral arterial disease.

Note: Acceptable documentation will include hospital discharge letters, operation notes or other clinical correspondence documenting performance of procedure & date.

A5.2.9 Emergency Hospitalisation for angina

Evidence of emergency hospital admission with chest pain considered due to angina pectoris, plus previous history of documented atherosclerotic coronary artery disease, or documented ischaemic ECG changes during admission, but not meeting criteria for acute myocardial infarction.

A5.3 SECONDARY ENDPOINTS

A5.3.1 All-cause mortality

Sum of all cardiovascular plus non-cardiovascular deaths.

A5.3.2 Fatal peripheral atherosclerotic events

Death occurring within 28 days from the onset of hospital-verified acute peripheral arterial atherosclerotic events. The diagnosis is based on symptoms, clinical findings and/or appropriate radiological investigations.

The Endpoints Committee will be responsible for the classification of all possible study endpoints. The Committee will receive all baseline and end of trial electrocardiograms showing serial changes, information regarding domiciliary visits or hospitalisation associated with possible endpoints, and information on all deaths.

A5.4 GLOSSARY

A5.4.1 Clinical classification of different types of myocardial infarction

Type 1
Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2
Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension
Type 3
Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new STelevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
Type 4a
Myocardial infarction associated with PCI

Type 4b
Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5
Myocardial infarction associated with CABG

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A5.4.2 Causes of elevations of troponin in the absence of overt ischemic heart disease
Cardiac contusion, or other trauma including surgery, ablation, pacing, etc.
Congestive heart failure—acute and chronic
Aortic dissection
Aortic valve disease
Hypertrophic cardiomyopathy
Tachy- or bradyarrhythmias, or heart block
Apical ballooning syndrome
Rhabdomyolysis with cardiac injury
Pulmonary embolism, severe pulmonary hypertension
Renal failure
Acute neurological disease, including stroke or subarachnoid haemorrhage
Infiltrative diseases, e.g. amyloidosis, haemochromatosis, sarcoidosis, and scleroderma
Inflammatory diseases, e.g. myocarditis or myocardial extension of endo-/pericarditis
Drug toxicity or toxins
Critically ill patients, especially with respiratory failure or sepsis
Burns, especially if affecting .30% of body surface area
Extreme exertion

A5.4.3 ECG manifestations of acute myocardial ischaemia (in absence of LVH and LBBB)
ST elevation
New ST elevation at the J-point in two contiguous leads with the cut-off points: ≥0.2 mV in men or ≥0.15 mV in women in leads V2–V3 and/or ≥0.1 mV in other leads.
ST depression and T-wave changes
New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads; and/or T inversion ≥0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1.

A5.4.4 ECG changes associated with prior myocardial infarction
Any Q-wave in leads V2–V3 ≥0.02 s or QS complex in leads V2 and V3.
Q-wave ≥0.03 s and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4–V6 in any two leads of a contiguous lead grouping (I, aVL,V6; V4–V6; II, III, and aVF).
R-wave ≥0.04 s in V1–V2 and R/S ≥1 with a concordant positive T-wave in the absence of a conduction defect.
The same criteria are used for supplemental leads V7–V9, and for the Cabrera frontal plane lead grouping.

Definitions of non-cardiovascular revascularisations:

Non-cardiac procedures
non coronary arterial surgery/intervention unspecified
arterial surgery unspecified
non coronary angioplasty +/- stent
fem-pop bypass/leg artery bypass
popliteal or femoral or iliac aneurysm repair
aortic aneurysm repair or stent
carotid surgery
cerebral artery aneurysm surgery or clipping
arterial graft reconstruction/excision (not dialysis access)
leg artery angioplasty +/- stent
renal artery angioplasty +/- stent
carotid angioplasty +/- stent
non coronary angiogram
angiogram of leg/femoral angiogram
renal artery angiogram

carotid angiogram or arch aortagram
Embolectomy

Amputations

amputation of leg
above knee amputation
below knee amputation
amputation of foot
amputation of toe
amputation of arm

APPENDIX 6: SAFETY OUTCOMES

Clinical laboratory safety parameters are shown below. Haematology and biochemistry will be performed at the local laboratories. All of the safety parameters are subject to routine regular monitoring for safety of the disease-modifying anti-rheumatic drugs (DMARDs). Such monitoring is required as part of routine clinical practice at intervals ranging between 2 weeks and 3 months for all but one DMARDs (the antimalarials). All patients will be questioned about muscle symptoms at each follow-up visit and if new and significant CK will be measured. Only serious adverse events will be recorded. Randomisation codes will be kept securely by participating pharmacists. If deemed necessary by the local investigator the randomisation code can be broken by contacting the local pharmacy.

Abnormalities of haematological and biochemical parameters in this population may be either due to DMARDs or the study drug. The decision of attribution will be left to the managing local investigator.

The study drug should be stopped if:

- Patient has new and significant muscle pains and CK>10xULN,Patient has new and significant muscle pains and ALT/AST >2xULN and CK between 3-10xULN and elevation persists upon re-testing.
- Myopathy is diagnosed (muscle pain or weakness AND CK >10 times ULN)
- Elevation of CK to ≥5 times ULN, persisting on retesting 1 week later, should also lead to discontinuation of study medication.

APPENDIX 7: INFORMATION ABOUT ATORVASTATIN

Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. Less than 2% of patients were discontinued from clinical trials due to side effects attributed to Atorvastatin.

The 'Summary of Product Characteristics' about Atorvastatin will be filed in the TRACE RA site file. Information about Atorvastatin can be found on the electronics medicines compendium section of the (www.emc.medicines.org.uk) website and detailed information about the side effects of the drug is also available in the British National Formulary .

Clinical Adverse Experiences (Please see 'Summary of Product Characteristics' for more details)

The most frequent (1% or more) adverse effects associated with Atorvastatin therapy, in patients participating in controlled clinical studies were:

Psychiatric disorders – Insomnia.
Nervous System disorders – Headache

Gastrointestinal disorders – Abdominal pain, dyspepsia, nausea, flatulence, constipation, diarrhoea

Musculoskeletal and Connective Tissue Disorders: Myalgia

General Disorders and Administration Site Conditions:

- Asthenia
- Elevated serum ALT levels have been reported in patients receiving Atorvastatin.
- Elevated serum CPK levels > 3 times upper normal (ULN) occurred in 2.5 % of patients on Atorvastatin compared with 3.1% with other HMG-CoA reductase inhibitors in clinical trials.

[Additional adverse events that have been reported in atorvastatin clinical trials are categorised below according to system organ class and frequency. Frequencies are defined as: very common (>10%), common (>1% and <10%), uncommon (>0.1% and <1%), rare (>0.01% and <0.1%) and very rare (0.01%)].

Organ/System Disorder	Event	Frequency
Metabolism & Nutrition	Anorexia Hypoglycaemia Hyperglycaemia	Uncommon Very rare Very rare
Nervous system	Dizziness Paraesthesia Peripheral neuropathy Dysgeusia	Common Uncommon Uncommon Very rare
Psychiatric	Amnesia Depression	Uncommon Uncommon
Blood and Lymphatic System	Thrombocytopenia	Uncommon
Immune System	Allergic reaction (including anaphylaxis	Common
Gastrointestinal	Anorexia Vomiting Pancreatitis	Uncommon Uncommon Uncommon
Hepatobiliary	Hepatitis Cholestatic jaundice Hepatic failure	Rare Rare Very rare
Skin & Subcutaneous Tissue	Alopecia Urticaria Pruritus Rash	Uncommon Uncommon Common Common
Musculoskeletal and Connective Tissue	Muscle cramps Myositis Rhabdomyolysis Myopathy Arthralgia Tendon rupture	Uncommon Rare Rare Uncommon Common Very rare
Eye Disorders	Visual disturbance	Very rare
Ear and Labyrinth Disorders	Tinnitus Hearing Loss	Uncommon Very rare
Reproductive system	Sexual dysfunction Gynaecomastia	Uncommon Very rare
General disorders	Chest pain Back pain Fatigue Angina Malaise Weight gain Peripheral oedema Angioneurotic oedema Interstitial lung disease	Common Common Common Common Uncommon Uncommon Rare Very rare Very rare

APPENDIX 8: POWER CALCULATION AND OTHER STATISTICAL CONSIDERATIONS

Table 1

Total number of patients with events and total number of events required for Cox regression (80% power at 5% significance level)

Reduction in Annual Event Rate (after adjustment for non-compliance)	Number of patients with events	Number of events*
20%	631	671
21%	565	597
22%	509	534
23%	460	481
24%	417	434
25%	379	393
26%	346	358
27%	317	327
28%	291	299

*assuming independence of events

Table 2

Expected total number of events for various combinations of annual event rate and patient-years of follow-up

Annual event rate*	Patient-Years Follow-up	1.3%	1.4%	1.5%	1.6%	1.7%	1.8%
	25000	325	350	375	400	425	450
	26000	338	364	390	416	442	468
	27000	351	378	405	432	459	486
	28000	364	392	420	448	476	504

*overall event rate in the two groups combined

APPENDIX 9: COMPOSITION AND ROLE OF TRIAL STEERING COMMITTEE AND DATA MONITORING COMMITTEE

A9.1 TRACE RA Trial Steering Committee (TSC) – Composition

The TSC membership should be limited and include an **independent** Chairman (not involved directly with the trial other than as a member of the TSC), two or more other independent expert members and the Chief Investigator. Where possible the membership should include a lay/consumer representative. Caroline Doré, the Arthritis Research UK's Senior Statistician, who is based at the MRC Clinical Trials Unit, should be invited to all meetings, in the role of observer. The trial manager, trial statistician etc should attend meetings as appropriate. Observers from **Arthritis Research UK** and Host Institution should be invited to all meetings.

Chairman: Professor Gordon Lowe, Emeritus Professor, Glasgow University

Independent Members:
Professor Jane Armitage, Professor of Clinical Trials and Epidemiology & Honorary Consultant, CTSU, University of Oxford
Professor Keith Fox, Professor of Cardiology, University of Edinburgh Centre for Cardiovascular Science
Professor Dorian Haskard, Director, Eric Bywaters Centre for Vascular Inflammation, Imperial College London

AR UK member:
Ms Caroline Doré, Senior Clinical Trial Statistician, AR UK

Lay member:
Ms Ailsa Bosworth, Chief Executive, National Rheumatoid Arthritis Society

Investigators:
Professor George Kitas, Consultant Rheumatologist, Dudley Group of Hospitals NHS Trust
Professor Jill Belch, Professor of Cardiovascular and Inflammation Medicine & Honorary Consultant Physician, Institute of Cardiovascular Research, Ninewells Hospital
Professor Deborah Symmons, Professor of Rheumatology and Musculoskeletal Epidemiology, University of Manchester

Secretary: Dr Hawys Williams, Clinical Trials Manager, University of Manchester

A9.2 TRACE RA Trial Steering Committee (TSC) –Role of the Trial Steering Committee:

It is **Arthritis Research UK's** policy that a Trial Steering Committee (TSC) should be set up for each of its multi-centre trials with the following terms of reference:

Terms of Reference:

1. To monitor and supervise the progress of the trial towards its interim and overall objectives including viewing the unblinded lipid differences during the study.
2. To review at regular intervals relevant information from other sources (e.g. other related trials)
3. To consider the recommendations of the Data Monitoring Committee (DMC)
4. In light of 1, 2 & 3, to inform **Arthritis Research UK** on the progress of the trial
5. To advise **Arthritis Research UK** on publicity and the presentation of all aspects of the trial.

The TSC provides overall supervision for the trial, and advice to the CI, **Arthritis Research UK** and the Host Institution on all aspects. The first meeting of the TSC should be held before recruitment to the trial begins, in order for the TSC to approve the protocol. Thereafter, the TSC should meet at least annually. The TSC should ensure that there are no major deviations from the trial protocol. The CI should call meetings of the TSC when there are any matters arising from the conduct or management of the trial that might require their advice.

A9.3 Data Monitoring Committee (DMC) – Composition

It is the sponsors' responsibility to decide whether a DMC is needed for a particular trial and if so to appoint one. The sponsors have agreed the composition of the DMC outlined below. The frequency with which the DMC meets will be dependent on the needs of the trial. The Chief Investigator (CI) should submit a detailed plan for the interim analysis before the trial commences. The plan must satisfy members of the DMC. Communication between the CI and the DMC chair is encouraged but should not bypass the TSC Chair.

The CI and the Chair of the TSC will agree with the DMC Chair a timely mechanism for reporting to the DMC. With the help of the trial statistician, the CI must provide blinded data, in strict confidence, to the DMCas frequently as the members of the sub-group request. Serious unexpected suspected adverse reactions must be reported to the lead clinician of the DMC and chairperson of the relevant multi-centre research ethics committee immediately. If appropriate, the MHRA (Medicines and Healthcare products Regulatory Agency) must also be informed.

Chairman: **Professor Michael Frenneaux**, Regius Professor of Medicine, University of Aberdeen

Members:
Dr Christopher Edwards, Consultant Rheumatologist, University of Southampton
Dr Jonathan Emberson, Senior Statistician, University of Oxford Clinical Service Unit
Professor Deborah Bax, Consultant Physician in Rheumatology, Clinical Director of Specialised Medicine, Royal Hallamshire Hospital, Honorary Professor of Rheumatology (University of Sheffield)

A9.4 Data Monitoring Committee (DMC) – Role

The DMC is the only body involved in the trial that has access to the unblinded comparative data. The role of the DMC is to monitor these data and make recommendations to the TSC on whether the trial should continue. Membership of the DMC should be completely independent of the CI, TSC and Host institution. The first meeting of the DMC should be held before recruitment to the trial begins, in order for the DMC to approve the protocol and ensure that appropriate arrangements have been made for review of the accumulating data and the results of any interim analyses.

Terms of Reference: DMC

1. To set up and maintain direct communication with the CI and Chair of the TSC. The Chair of the TSC should be made aware of all communications between the CI and DMC sub-group.
2. To receive a copy of the trial protocol and plans for interim analysis prior to commencement of the trial, or, in the case of the first wave of trials, as early as possible.
3. To receive reports (as per template in Appendix 3) during the trial at intervals agreed with the TSC and CI. It would be expected that these would be 6 monthly in the first year, and no less frequent than 12 monthly after that.
4. If interim analysis of the trial data is not planned in the protocol the sub-group should determine whether interim analysis should be undertaken
5. To consider data from interim analyses, unblinded if considered appropriate, plus any additional safety issues for the trial and relevant information from the template and other sources
6. In the light of 3, 4 & 5, and ensuring that ethical considerations are of prime importance, to report to the TSC and recommend on the continuation of the trial.

APPENDIX 10: TRIAL EVALUATIONS SCHEMA

***** DAS - TRACE RA DAS REQUIREMENTS

Trial Investigations	Visit 1		Visit 2	Visit 3	Visit 4		Visit 5	Visit 6		Visit 7, 9, 11, 13,	Visit 8, 10, 12, 14, 16
	Baseline		Month 3	Month 6	Month 12		Month 18	Month 24		Month 30, 42, 54, 66,78	Month 48, 60 , 72, 84
	ALL	DAS	**ALL**	DAS	**ALL**	DAS	**ALL**	**ALL**	DAS	**ALL**	**ALL**
Inclusion/Exclusion Criteria Assessments	✓	#									
Written Informed Consent	✓	#									
Height, Weight, BP	✓										
Medical History	✓										
Concomitant Medication	✓		✓		✓		✓	✓		✓	✓
ESR/CRP, RhF/anti-CCP, LFTs at baseline and LFTs at follow up visit	✓				✓		✓	✓		✓	✓
Research DNA blood sample (BioBank)	✓										
Research serum and plasma (BioBank) *	✓										
Research RNA sample (DAS)		#		#							
Research serum and plasma (DAS)		#		#							
Discussion of CVD risks	✓										
HAQ	✓			#	✓			✓			✓
EQ5D	✓			#	✓			✓			✓
Lifestyle Questionnaire	✓										
DAS 28 Tender & Swollen joint count	✓			#		#			#		
Patient Global Assessment (VAS)	✓			#		#			#		
Nurse Global Assessment (VAS)		#		#		#			#		
Check for Serious Adverse events &Cardiovascular events			✓		✓		✓	✓		✓	✓
Drug compliance			✓		✓		✓	✓		✓	✓

- Research serum and plasma sample for TRACE RA BioBank is not required if patient is enrolled in TRACE RA DAS

APPENDIX 11: AMENDMENTS TO THE STUDY PROTOCOL

Appendix 11.1: The following changes have been incorporated into Version 2 (dated 27th July 2007) of the protocol

- The title page footer updated to new date and version
- Changes to Trial Management Team: Trial Manager changed from Ms Sumitra Smith to Dr Hawys Williams. Regional trials co-ordinators added (Ms Rebecca Storey and Mrs Shobna Vasishta)
- Changes to Trial steering committee details: Secretary changed from Ms Sumitra Smith to Dr Hawys Williams
- Endpoints Committee: Chairman (Professor Stuart Cobbe) appointed and details added.
- TRACE RA DAS substudy: Following advice from the Trial Statistician, it was decided that X-rays would be omitted from Version 2 of the trial protocol. This was based on a Power Calculation identifiying that no changes would be detectable by performing X-rays at baseline and 24 months.
- TRACE RA DAS substudy: changes to sample volumes collected at baseline and at 6 months to reflect collaboration with Pfizer to create TRACE RA DAS Biobank
- TRACE RA Biobank: changes to sample volumes collected at baseline to reflect collaboration with Pfizer to create TRACE RA Biobank
- Section 5: Eligibility. Adequate Contraception. Additional information added with regards to methods of adequate contraception.
- Section 6.2.3, Follow up visits for TRACE RA participants: Addition of Liver function test (LFT) to be included as part of 3 month drug compliance/safety visit.
- Section 10.8: Deletion of p values**:** Independent DMC enquired if a p value of <0.0005 was valid or if this was a typing error."As stated in section 10.8 of the trial protocol there is no formal stopping rule for this study. The p value of <0.0005 was supposed to be a guide as to when the trial should definitely be discontinued: it was not intended that p values > 0.0005 should be used as justification for continuing the trial. It was assumed that the DMC would consider all the available evidence when making such a decision. Rather than changing this value to <0.005, we would prefer to remove the whole sentence from section 10.8, as it is obviously open to misinterpretation."
- Appendix 9: Composition and role of Trial Steering Committee and Data Monitoring Committee:

  Composition altered to reflect changes in representatives.

Appendix 11.2: The following changes have been incorporated into Version 3 (dated 1st August 2008) of the protocol.

- The title page footer updated to new date and version
- Changes to Trial Team: Project Assistant changed from Ms Nicola Dale to Ms Donna Kempson.
- Data Monitoring Committee: Professor Michael Frenneaux added.
- Endpoints Committee: Professor David Stott, Professor Roger Sturrock and Professor Peter Macfarlane added.

- Main trial schema: Amended to clarify that patients withdrawn from the trial should continue to be followed up annually. This includes patients following a CV event.

- Section 6.1. Patient selection and informed consent: Clarification that centres do not have to fax registration forms prior to randomisation, as original protocol version implied. Centres are requested to fax the registration forms after randomisation.

- Section 6:2.1 Baseline/randomisation visit: Clarification that routine blood test results can be used up to 6 weeks prior to randomisation for trial screening.

- Section 7. Study withdrawal: Clarification that patients withdrawn due to experiencing a cardiovascular event will continue for annual follow up visits as well as flagging for mortality.

- Section 8. Drug supplies and labelling: Change of 'Cardinal' to 'Catalent' to reflect supplier's name change.

- Appendix 3. Sample Patient Information Sheet, Consent Forms and GP Letters: following additional documents added:
    - Patient Information Leaflet and Consent Form - DNA collection only
    - GP letter for centres that routinely assess for 10 year cardiovascular disease risk
    - GP letter for centres that DO NOT routinely assess for 10 year cardiovascular disease risk
    - GP referral letter

- Appendix 5. Definition of Cardiovascular Endpoints: This section has been re-written by the Chair of the Endpoints Committee to provide further clarification of the endpoints and to adopt the Universal Definition of Myocardial Infarction (Thygesen et al; 2007).

- Appendix 7. Information about Atorvastatin: This section has been amended to incorporate new information published by Pfizer (Summary of Product Characteristics dated 10 December 2007) and also the Drug Safety Update publishes by the MHRA (February 2008) reporting that additional side-effects (sleep disturbances, memory loss, sexual dysfunction, depression, and interstitial lung disease) have been recognised with statins.

Appendix 11.3: The following changes have been incorporated into Version 4 (dated 3rd March 2010) of the protocol

- Section 7. Study withdrawal: Clarification that patients can re-commence trial medication and insertion of guidance on blood tests required prior to re-commencing and thereafter.
- Chief Investigator and statistician Protocol approval and Principal Investigator declaration pages inserted.
- Appendix 2.3 TRACE RA Biobank, A2.3 Methodology b. Sample handling and DNA extraction: Amendment to clarify Biobank blood samples taken as part DAS substudy.
- DAS substudy: DAS score entry criteria reduced from ≥4.4 to ≥3.2
- Addition of Pfizer Representative to membership of the Biobank Repository Committee
- Amendment to Professor Lowe's professional title to reflect his retirement from medical practice in 2009.
- Amendment to start and end dates for trial.

Appendix 11.4: The following changes have been incorporated into Version 4.1 (dated 6th May 2010) of the protocol

- Section 6.2.2. Allocation of patients to trial treatment arm: following changes to the DAS substudy entry criteria and consultation with the TSC, the requirement for separate labelling of DAS substudy medication was no longer deemed necessary. This is as the number of patients randomised to each arm is expected to be equal if centres as DAS substudy patients will be randomised sequentially. This section of the protocol was amended to reflect this.
- Section 9.5. Changes to causality assessment - addition of 'related' as one of the criteria and removal of 'unlikely to be related'.

- Entire document updated with change of name of Arthritis Research Campaign to Arthritis Research UK to reflect change of name of charity (March 2010)
- Appendix 9: Composition and role of Trial Steering Committee and Data Monitoring Committee: Composition altered to reflect changes in DMC membership.
- Appendix I & II amended in light of Biobank samples no longer being automatically shared with Pfizer.

Appendix 11.5: The following changes have been incorporated into Version 5 (dated 6th December 2010) of the protocol

Summary of Key Points:

- Trial recruitment has been extended to March 2014 with the last follow-up appointment being in March 2016, or until a sufficient number of events has accrued to provide statistical power whichever is the earlier. Recruitment target amended to more than 4000 patients.
- Number of participating centres increased from 100 to 120
- New Power calculations (based on observed recruitment and number of events) and subsequent increase in required sample size.
- Revision of Endpoints to include non-coronary revascularisations, TIA and exclude angina and haemorrhagic stroke
- Pharmacovigilance procedures amended to exclude reporting of adverse events unless an adverse reaction is deemed to have a reasonable causal relationship with atorvastatin. Procedures also amended to provide further guidance on management of patients with new and significant muscle pains.
- Case Report form and blood tests have been simplified
- Patient Information Leaflet - Main trial amended in light of protocol amendment and format designed to make it more visually appealing.
- Patients' addresses to be collected retrospectively and prospectively
- Co-Sponsor (University Of Manchester) representative amended from Dr Karen Shaw to Prof. Nalin Thakker

Detailed Description of Protocol Changes:

- Trial Contacts, Page 2: Trial contacts amended in light of Miss Donna Watson and Miss Donna Kempson leaving the trial team and Dr Emma Knox being appointed as Trial Co-ordinator (Manchester CTU)
- TSC Committee Membership, Page 3: Removal of Prof Cobbe as member of TSC, following his retirement. Amendment to Jane Armitage's title from Dr to Professor
- Trial Schema, Page 6: Amendment to trial schema in accordance with changes in study visits (please see below).
- Section 3.1 (Primary Endpoints), page 11: Primary endpoints amended to include non-coronary revascularisations, TIA and exclude angina and haemorrhagic stroke
- Section 3.2 (Secondary and Tertiary Endpoints), page 11: Secondary endpoints refined to focus on coronary events and Tertiary endpoints added.
- Section 4 (Study Organisation), page 12: Number of patients randomised increased from 3800 to at least 4000 and number of participating centres increased from 100 to 120.
- Section 5 (Eligibility), page15: List of contra-indicated drugs updated according to the SmPC and data from other statin trials.
- Section 6.1: (Patient selection and informed consent) page 15: Addition of pre-printed patient detail logs to procedures to facilitate tracking of data.
- Section 6.2.1 (Baseline/randomisation visit) page 15: Removal of family history of cardiovascular disease, baseline ECG and measurement of waist circumference. ESR/CRP test results can be used within the last 6 weeks if patient's is stable and treatment unchanged. RhF +/or anti-CCP can also be used from previous timepoints. Removal of routine haematology and biochemistry blood tests. Removal of random glucose blood test and CK measurement. Removal of collection of data for ONS flagging for mortality of ineligible and eligible but not participating in the trial.
- Section 6.2.3 (Follow up visits for TRACE RA participants), page 16: Previously patients were asked to attend clinic for annual appointments with prescriptions every 6 months. The protocol has been amended to request identical 6 monthly follow-up, which can be conducted by telephone if necessary

or in their home if required. ECG taken at the end of trial removed. The management of patients whom indicate presence of new and significant muscle symptoms has been revised.

- Section 6.4: (End of trial) page 19: Addition of plan to continue recruiting until March 2014 with last follow-up in March 2016, or until a sufficient number of events has accrued to provide statistical power.
- Section 7 (Discontinuation of study medication), page 20: This section was previously entitled 'Study withdrawal' and has been revised to provide clarity that as the trial will be analysed on an intention to treat analysis, patients are asked to continue to be followed up to the end of trial, regardless of whether they remain on the study medication. Patients are also able to recommence on study medication at any time provided liver function tests (ALT/AST) are within the screening limits.
- Section 8.2 (Supply of study medication to centres) page 20: All study medication packs for new patients will comprise of 6 monthly supply, instead of previously supply them with 3 month supply at baseline and 3 month visit. The 3 month study visit will remain.
- Section 9.1 (Cardiovascular outcomes and reporting of cardiovascular outcomes) page 21: A single SAE form will be used for the reporting of cardiovascular endpoints and other SAEs.
- Section 9.2 (Serious adverse events) page 21: Elective rheumatological procedures will now be reported as serious adverse events.
- Section 9.3 (Adverse events) page 21: Unless leading to discontinuation of study treatment, adverse events are not required to be recorded on the Case Report Form. Procedures for management of patients presenting with new and significant muscle pains added.
- Section 9.6 (Reporting of SAEs, SARs and SUSARs to Pfizer) page 22: Reporting requirement of SAEs to Pfizer added.
- Section 9.7 (Recording and reporting of all SAE/SARs) page 23: Flow diagram amended in light of changes in previous sections.
- Section 10.1 (Sample size) page 24: The sample size has been re-calculated by the trial statistician based on recruitment rates in the first 3 years and observed event rates during this period.
- Section 10.2 (Planned recruitment rate) page 24: Number of recruiting centres increased from 100 to 120, with required number of patients recruited by March 2014.
- Section 10.3 (Compliance): page 26: Compliance to study treatment will be measured by asking the patient instead of tablet count.
- Section 11.1 (Assessment of efficacy outcomes) page 26: Addition of procedure for censoring of patients from study medication if they experience a cardiovascular endpoint or develop condition for which statin therapy clearly indicated.
- Section 11.2 (Assessment of safety) page 26: Clarification of procedures for patients presenting with new and significant muscle pains.
- Section 12.7 (Financial matters) page 30: Details of UKCRN adoption of trial and its substudies added.
- Section A2.3 (Biobank Methodology) page 40: Increase in number of patients recruited to Biobank from 3808 to more than 4000.
- Section A3 (Sample Patient Information Sheet, Consent Forms and GP letters) page 44: Removal of Patient Information Leaflet: ONS Flagging, GP letter for ONS flagging consent from non-participants, GP letter for withdrawn patients.
- Section A5 (Definitions of cardiovascular endpoints) page 46-51: Primary endpoints amended to include non-coronary revascularisations, TIA and exclude angina and haemorrhagic stroke. Secondary endpoints refined to focus on coronary events and Tertiary endpoints added. Definitions of non-coronary revascularisations added.
- Section A6 (Safety Outcomes) page 52: Actions to be taken on presentation new and significant muscle pains and elevation CK added.
- Section A8 (Power calculations and other statistical calculations) page 55: Amended in light of statistical remodelling of trial statistics based on observed recruitment and event rate to date.
- Section A9.1 (TSC Committee Composition), page 56: Removal of Prof Cobbe as member of TSC, following his retirement. Amendment to Jane Armitage's title from Dr to Professor
- Section A10 (Trial Evaluation Schema) page 58: Amended in light of changes to previous sections of protocol (i.e removal of baseline and end of trial ECGs, removal of baseline routine haematology and biochemistry, removal of measurement of waist circumference and family history of cardiovascular disease, all patients to be followed up every 6 months etc)