UNIVERSITY OF LEEDS

NIHR
Leeds Musculoskeletal
Biomedical Research Unit

CADERA: Quantitative MRI to define mechanisms of cardiovascular co-morbidity in patients with early Rheumatoid Arthritis and to measure the effect of biological therapy

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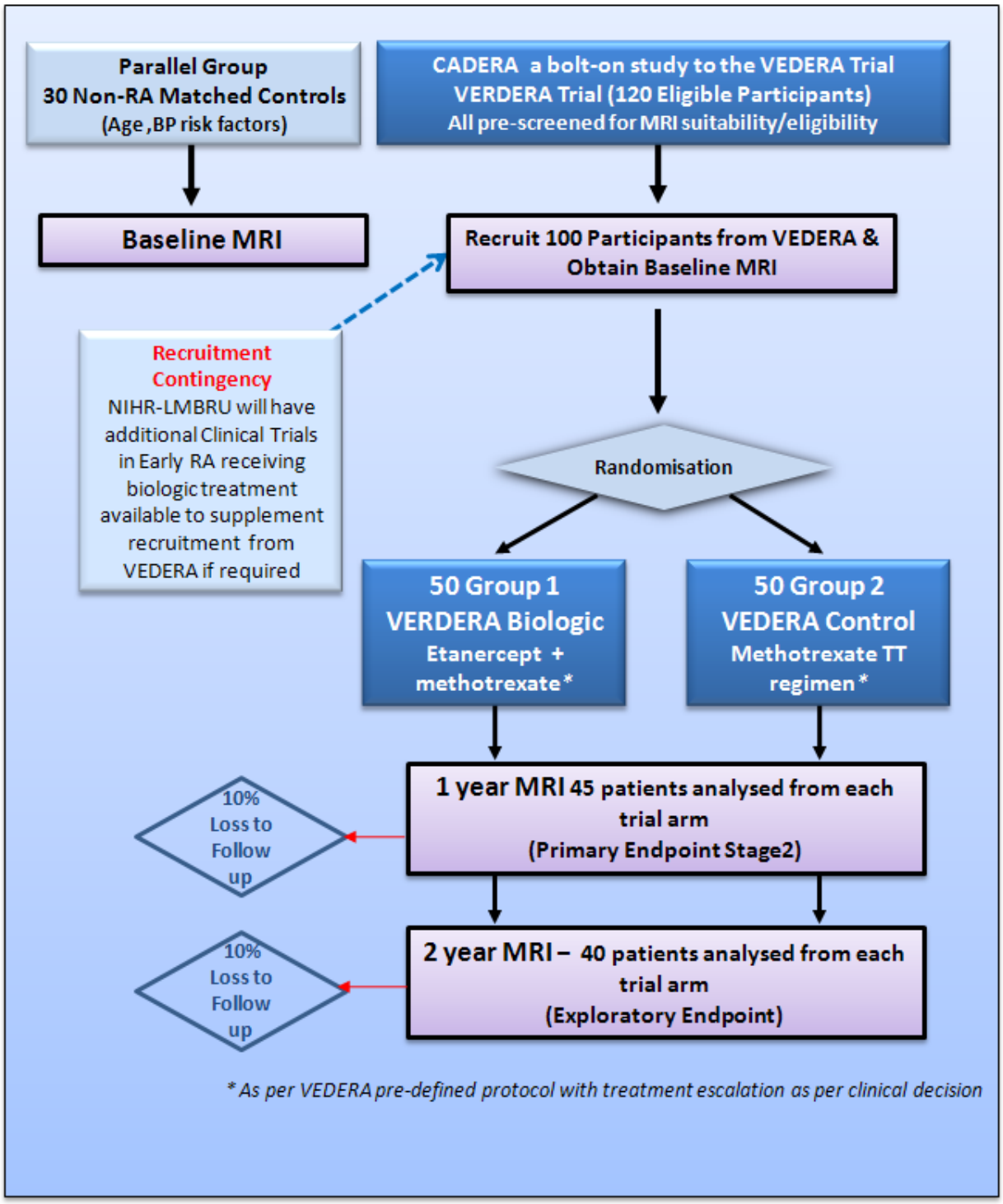
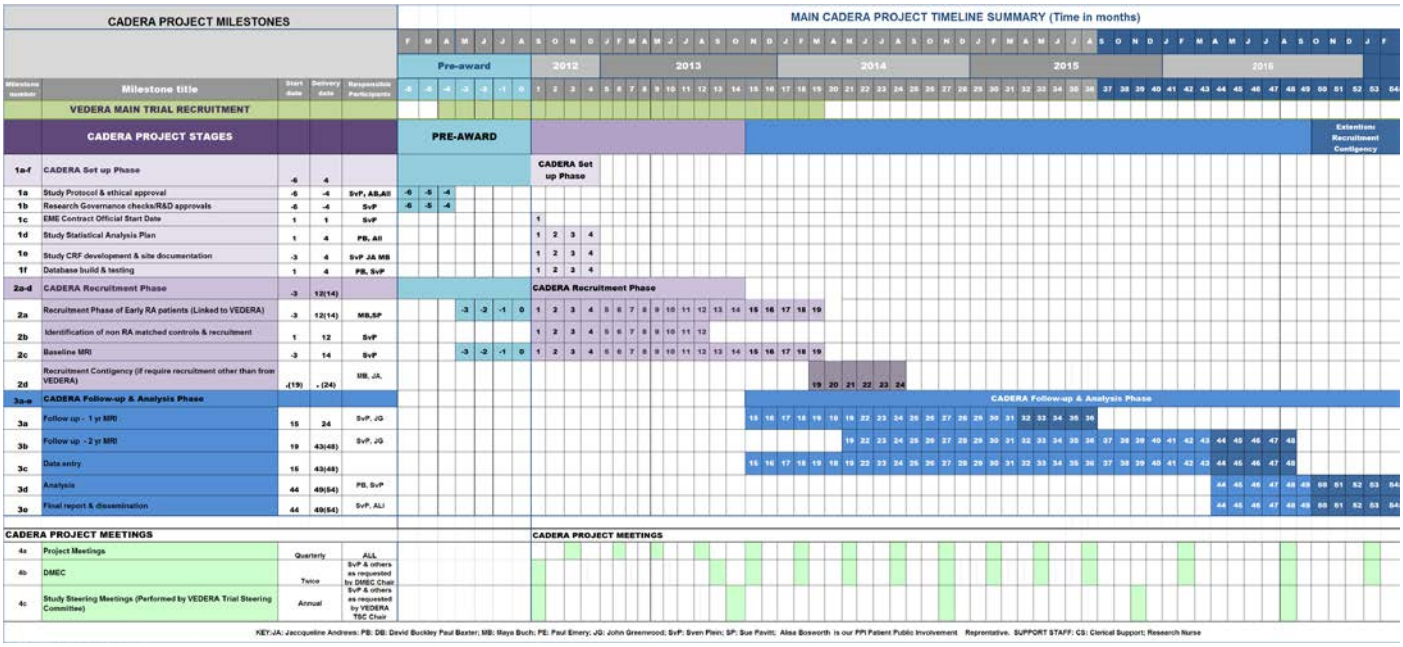
3. STUDY FLOW DIAGRAM AND GANT CHART

3.1 Flow diagram



3.2 Gantt chart



4. GLOSSARY OF TERMS AND DEFINITIONS

TABLE 1: ACRONYMS / ABBREVIATIONS			
ACRONYM	DEFINITION	ACRONYM	DEFINITION
ACR	American College of Rheumatology	MBF	Myocardial blood flow
AE	Adverse Events	MPV	Myocardial perfusion reserve
anti-TNF	Anti-tumour necrosis factor	MTX	Methotrexate
CIMT	Carotid Intima-Media Thickness	NIHR	National Institute of Health Research
CLRN	Comprehensive Local Research Network	NIHR LMBRU	NIHR Leeds Musculoskeletal Biomedical Research Unit
CSG	Clinical Studies Group	PET	Positron emission tomography
CVD	Cardiovascular disease	PIL	Patient Information Leaflet
DMARDs	Disease modifying ant-rheumatic drugs	PPE	Patient Public Engagement
DMEC	Data Monitoring Ethics Committee	PPI	Patient Public Involvement
ECV	Extra-cellular volume	QA	Quality Assurance
ETN	Etanercept	RA	Rheumatoid arthritis
EULAR	The European League Against Rheumatism	SSC	Study Steering Committee
FTE	Full Time Equivalent	SMG	Study Management Group
IA	Inflammatory arthritis	SSC	Study Steering Committee
IACON	Inflammatory arthritis disease continuum: longitudinal cohort study in inflammatory arthritis	T2DM	Type 2 diabetes mellitus
IMID	Immune Mediated Inflammatory Diseases	TNF	Tumour Necrosis Factor
MRI	Magnetic Resonance Imaging	TT	Treat to Target
Leeds IACON	Leeds Inflammatory Arthritis Disease Continuum	VEDERA	Very Early vs Delayed Etanercept in Rheumatoid Arthritis Study (phase IV randomised trial assessing anti-TNF agent in patients with early RA)
LV	Left ventricle		

5. BACKGROUND

5.1. Existing Research

5.1.1. Health problem: Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease which affects approximately 400,000 people in the UK. Although its primary manifestations are musculoskeletal, RA is a systemic condition with common extra-articular manifestations involving the cardiovascular, cutaneous, pulmonary and ophthalmological systems. Life expectancy of patients with RA is reduced and mortality increased up to three-fold compared to the general population. This is largely due to increased frequency of premature CVD (Kaplan 2006), which constitutes up to 40% of mortality in RA patients and is as high as that of patients with other major CVD risk factors such as Type 2 diabetes mellitus (Gonzalez 2007). It is now widely accepted that CVD risk in RA is independent of and incremental to traditional CV risk factors (del Rincon 2001). Recent European guidelines (Peters 2010) therefore suggest that, pending more definitive evidence, estimates of CVD risk are multiplied by a factor of 1.5 for patients with RA.

5.1.2. Mechanisms of CVD in RA: While it is likely that several mechanisms are responsible for the increased CVD risk in RA, the predominant underlying pathological process is thought to be immune dysregulation leading to systemic inflammation (Pasceri 1999). The inflammatory process, mediated significantly through pro-inflammatory cytokines such as tumour necrosis factor (TNF) is linked to atherosclerosis and plaque rupture and has confounding effects on lipid and glucose metabolism, blood pressure and haemostatic factors (Libby 2008). Supporting this concept is the observation that markers of RA severity such as rheumatoid factor and erythrocyte sedimentation rate are strongly associated with adverse CV outcomes in RA (Hannawi 2007). Also, atherosclerosis itself is increasingly views as an inflammatory-mediated process (Libby 2002) and in general CVD populations, levels of inflammatory biomarkers are associated with worse outcome. Clinical studies have demonstrated a wide range of cardiovascular manifestations of RA, many associated with disease activity (Aubury 2007):

5.1.2.1. Arterial stiffness: Arterial stiffness is a strong surrogate marker for CVD risk in patients with a range of co-morbidities (Meaume 2001). It can be measured by pulse wave velocity or as distensibility of the aorta by ultrasound and Magnetic Resonance Imaging (MRI), but requires careful correction for age and blood pressure. Mäki-Petäjä (2006) analysed 77 patients with RA without traditional cardiovascular risk factors and found aortic pulse wave velocity to be higher than in controls (8.35 (95% CI 7.14 to 10.24)m/s versus 7.52 (95% CI 6.56 to 9.18)m/s respectively, p=0.005) and correlated with age, mean arterial pressure and C-reactive protein.

5.1.2.2. LV function: Echocardiography studies have shown that patients with RA have high rates of diastolic dysfunction (Liang 2010), heart failure (Nicola 2005 and Nicola 2006) and heart failure with preserved ejection fraction (Davis 2008). The mechanisms for these observations are not completely understood, but are thought to involve microvascular disease or changes in the extracellular compartment such as an extended extracellular matrix, caused by chronic inflammation.

5.1.2.3. Myocardial perfusion: Following anecdotal reports of impaired myocardial perfusion in patients with RA, a positron emission tomography (PET) study measured myocardial blood flow (MBF) reserve in 25 patients with RA or Systemic Lupus Erythematousus (SLE) and age matched controls (Recio-Mayoral 2009). In all patients coronary arterial disease was excluded by angiography. Significantly lower MBF reserve was observed in RA patients (2.44 +/- 0.78 vs. 3.81 +/- 1.07; $P < 0.001$) and was inversely related to disease duration ($r = -0.65$; $P < 0.001$). Similar to the studies demonstrating contractile dysfunction, these findings are consistent with the concept of microvascular pathology due by prolonged systemic inflammation in RA, which may precede and contribute to the effects of coronary artery disease in RA patients.

5.1.2.4. Atherosclerosis: Carotid Intimal-Media Thickness (CIMT) is considered a surrogate marker of CVD (Mancini 2004). A meta-analysis of 22 studies with a total of 1384 patients with RA and 1147 controls found that RA patients had a greater CIMT than controls with a mean difference in CIMT between the groups of 0.09mm (95% CI: 0.07-0.11mm) (van Sijl 2011). There is emerging evidence that CIMT is abnormal even in those diagnosed with early RA of less than 12 months duration, correlating with tender and swollen joint counts, as well as age and systolic blood pressure (Chatterjee 2011).

5.1.3. Contemporary treatment of RA: Early diagnosis of RA and immediate intervention with conventional disease modifying anti-rheumatic drugs (DMARDs) is an established practice; the concept of a treat to target approach (regular, tight control of disease activity with titration of therapy towards achieving pre-defined target

of remission where feasible) was recently encapsulated in the publication of international recommendations (Smolen 2010). More recently, biologic therapies have transformed the management of patients with RA. As first suggested by our group (Conaghan 2002), early first line treatment with biologics may have additional beneficial effects over DMARD therapy by interrupting progression along the RA disease continuum. However, current practice as recommended by NICE remains unsupportive of first-line aggressive biologic therapy.

5.1.4. Effects of RA treatment on RA co-morbidity: The benefits of anti-inflammatory therapy in RA may extend beyond the effects on the synovial pathology and may reduce cardiovascular morbidity and mortality. Several studies have reported improvements in surrogate markers of CVD in response to anti-inflammatory therapy. Aortic stiffness has been shown to improve in response to TNF alpha blockade (Angel 2010) and interleukin-1 antagonists (Iakonmodis 2008). Clinical trials of anti-TNFα treatments in RA have been challenging because of the relatively small number of hard clinical endpoints in the study populations (Westlake 2010). For example, the TRACE RA trial recruited 3001 participants to measure efficacy of Atorvastatin for the primary prevention of cardiovascular events in patients with RA but was stopped early (ttp://www.dgoh.nhs.uk/tracera/default.aspx). Observational studies have suggested that anti-TNFα treatment reduces cardiovascular endpoints, but because of the small numbers of events were not able to adjust for important confounders and could not differentiate between cardiovascular events that follow different pathophysiological pathways (Jacobbson 2005). Because in current practice anti-TNFα treatment is reserved for patients with the most advanced disease, observational studies are inherently are limited by a selection bias towards high-risk patients. Importantly, in patients with established CVD, aggressive anti-inflammatory may even have a deleterious effect (Chung 2003). Aggressive anti-inflammatory therapy therefore appears to provide a "window of opportunity" in the early stages of RA by interrupting progression along the RA disease continuum with the potential to significantly impact CVD risk.

5.1.5. Cardiovascular MRI: Cardiovascular MRI is widely recognised as a safe, sensitive, reproducible and comprehensive non-invasive imaging test to detect CVD. With cine MRI, LV mass and function can be measured more accurately than with any other imaging method (Bellenger 2000). Similar cine methods or phase contrast MRI can be used to measure aortic distensibility (Lee 2007). MRI with tissue tagging provides accurate measurements of regional and global myocardial strain as an early marker of contractile dysfunction (Ibrahim 2011). Dynamic contrast enhanced MRI methods combined with quantitative analysis can be used to estimate myocardial blood flow (MBF) at rest and during hyperaemic stress (Jerosch-Herold 1998). Myocardial perfusion MRI has demonstrated reduced MBF reserve in asymptomatic adults with CVD risk factors, suggesting it can detect preclinical pathology (Wang 2006). Due to its high spatial resolution, myocardial perfusion MRI can detect microvascular disease patterns of ischaemia, which preferentially affect the subendocardial layers (Panting 2002). T1 mapping MRI methods are increasingly used to measure the extent of the extracellular matrix in the heart, which expands in response to inflammation and fibrosis (White 2012). Importantly, MRI has no harmful effects on the human body and all the measurements listed above can be combined in a single imaging protocol (Lee 2007).

5.1.6. Cardiovascular MRI in RA: The literature on cardiovascular MRI in RA is sparse. In contrast to previous echocardiography studies, Giles et al showed using MRI that patients with RA have reduced (rather than as anticipated higher) LV mass than non-RA controls and reduced LV ejection fraction (Giles 2010). Higher levels of RA specific antibodies and current use of biologic agents were associated with lower LV mass but not lower EF. The authors speculate that these observations are related to chronic inflammation and microvascular hypoperfusion resulting in myocyte loss and/or fibrosis in patients with RA. This suggestion is consistent with the observation of reduced myocardial perfusion reserve in RA in a previous PET study (Recio-Mayoral 2009). Similar data have been produced in a separate study of 24 RA patients (Puntmann 2010) which also demonstrated increased signal on T2 weighted MRI suggestive of chronic oedema due to inflammation. Other studies have used MRI to delineate atherosclerotic plaque in RA (Furer V 2012). No previous studies have combined macrovascular, microvascular and detailed myocardial assessment by MRI in RA and the full potential of MRI for a comprehensive and quantitative evaluation CVD in RA has not yet been realised.

5.1.7. Local studies in RA: The NIHR Leeds Musculoskeletal Biomedical Research Unit (LMBRU) incorporates a designated Cardiovascular Disease in Immune Mediated Inflammatory Diseases (IMID) Clinical Research Group. This provides access to patient cohorts, clinical trials and infrastructure for longitudinal follow-up of CV events in RA cohorts. Specifically we have agreed access to:

5.1.7.1. The IACON Study: A landmark event in the development of the LMBRU CVD in IMID work stream was the creation in June 2010 of a major new longitudinal cohort study in inflammatory arthritis (IA), the IACON (Inflammatory Arthritis disease CONtinuum) study. This facilitates collection of CVD outcome measurements in patients with IA at Leeds from disease inception onwards – *the IACON longitudinal cohort study* - examining CVD outcomes in IA (led by Dr Jacqueline Andrews). The current proposal can benefit from this set-up, as all study patients will enter IACON, permitting continued follow-up after the completion of the study.

5.1.7.2. The VEDERA trial: To further clarify the degree of benefit of first-line biologic therapy in RA, the VEDERA (Very Early versus Delayed Etanercept in Rheumatoid Arthritis) study was designed (PI Dr. Maya Buch). This is a phase IV single-centre randomised, parallel group, open-label study, to compare depth of remission and immunological normalisation induced by first line anti-TNF versus optimal conventional DMARD in patients with early, treatment-naïve RA (see section 4.2 for details). Using limited local funding, we have negotiated to commence cardiovascular MRI (acquisition-only) for the current proposal on patients recruited to VEDERA; continued cardiovascular MRI acquisition & analysis is dependent on a successful outcome of this proposal.

5.1.8. Pilot work and proof of principle

5.1.8.1. Knowledge transfer of MRI Protocol: Our group has a very strong track record in cardiovascular MRI. We have shown in a large study of patients with suspected angina that MRI can detect myocardial ischaemia with greater sensitivity than nuclear perfusion imaging (Greenwood 2012). We have developed methods for high-resolution (1mm in plane resolution) myocardial perfusion MRI methods, which allow us to study separate myocardial layers in greater detail than with previous methods (Plein 2008). Capitalising on this increased spatial detail, we have developed novel post-processing methods, which quantify time-dependent transmural myocardial perfusion gradients and hold particular promise in microvascular disease (Houtvast 2011). We have pioneered multi-component MRI protocols for the comprehensive evaluation of patients with ischemic heart disease and cardiomyopathy (Plein 2002). In an ongoing programme of research (BHF Senior Clinical Research fellowship to Plein), we are applying MRI to patients with type 2 diabetes mellitus (T2DM) and pre-diabetes and are detecting a significant reduction in MBF reserve and increased resting MBF compared with controls (Larghat 2012). The MRI protocols we have developed in ischaemic heart disease are therefore suitable for translation to other clinical cohorts with CV risk factors.

5.1.8.2. Proof of Concept: We have performed a pilot study using the proposed MRI protocol in 10 patients with RA (disease duration 20+/-9.6 years). Patients were matched by age and gender to 10 asymptomatic subjects without RA. The protocol was competed in all 10 subjects in 64 +/- 8 minutes on a 3 Tesla Philips Achieva MRI system. MBF reserve was 2.6 +/- 0.6 in RA patients, compared with 3.4 +/- 1.1 in matched controls (p=0.08). Aortic distensibility was significantly different with a mean and standard deviation of $1.83\pm0.4cm^2$ vs. $2.6\pm0.6cm^2$ in controls. LV volumes and mass were similar between groups and LV strain and twist showed trends towards a reduction in RA patients, but without reaching statistical significance. This pilot study confirms that our comprehensive MRI protocol can be applied to patients with RA and detects a range of cardiovascular pathologies. In patients with advanced RA, significant differences of some MRI markers of CVD can be detected even in a small study population.

5.1.8.3. Reproducibility: The MRI measurements in this proposal have been validated in previous reproducibility studies. In our hands, the intra-observer coefficient of variability (CoV) is 8% for aortic distensibility and 9% for aortic arch pulse wave velocity (n=17), with an inter-study CoV of 17% for distensibility and 19% for pulse wave velocity (Oliver 2012). Myocardial perfusion reserve by Fermi-deconvolution has an intra-observer CoV of 19%, inter-observer CoV of 29% and inter-study CoV of 29% (Larghat 2010). Analysis of tagged MRI images shows an intra-observer CoV for circumferential strain of 4.3% and 1.2% for LV twist (n=12). Inter-study CoV of circumferential strain is 3.7% and 9.6% for LV twist (Swoboda 2012). Extracellular volume fraction has an interstudy CoV of 17% and 14% for rest and stress, respectively (Broadbent 2012). These pilot data show that quantitative MRI measurements are robust and suitable for longitudinal assessments.

5.2. Risks and Benefits

5.2.1. Risks: MRI is a standard clinical imaging modality in every day clinical use and risks to the study participants

from MRI scanning are very small. Contraindications for MRI are the presence of certain metallic objects, electrical devices and severe claustrophobia. Patients with any such contraindications will not be included in the study. Importantly, the VEDERA study includes musculo-skeletal MRI so that the recruitment population for CADERA is pre-screened for MRI contraindications. Adenosine stress agents carry a small risk of adverse effects including transient atrio-ventricular block and bronchospasm. Patients at increased risk of such side-effects (known asthma or greater than first degree atrio-ventricular block) will be excluded from the study. MRI contrast agents carry a very low risk of allergic reactions (~1:10,000); patients with known allergies to MRI contrast agents will not be recruited. Because of concern over the development of nephrogenic systemic fibrosis relating to some MRI contrast agents, patients with renal failure and an estimated glomerular filtration rate of less than 30 ml/min/1.73m^2 will not be recruited. The cardiac MRI department in Leeds has safely performed several thousand stress MRI scans and is fully equipped to deal with any potential complications. The Division of Rheumatic and Musculoskeletal Disease has conducted several studies that have included musculoskeletal MRI in patients with early and advanced RA. Good patient acceptability has been observed and so we do not anticipate MRI being a barrier to patient recruitment. In the pilot phase, no specific problems were encountered in patients with RA and all patients completed the study.

5.2.2. Benefits: Because the recruited patients (section 4.4) are part of a clinical trial (VEDERA) they will receive close clinical supervision through that trial. For the proposed project, MRI scanning may demonstrate incidental findings that require investigation or treatment. Our patient advisors have told us that most patients would consider this a benefit, although we appreciate the concern that incidental findings can cause.

5.2.3. Risk to benefit ratio: The risks for participants in this study are very small while the potential benefits of this study are substantial, both in terms of mechanistic insight as well as in terms of potential impact on CVD risk in patients with RA.

5.3. Rational for current study

5.3.1. Current knowledge gaps in RA: Although excess CVD risk in RA is now well recognised, there remain major knowledge gaps in the understanding of its mechanisms and optimal management. A distinct RA phenotype that is at higher risk of future CVD has not been identified. The underlying mechanisms of CVD and the different CVD manifestations (including macrovascular, microvascular and myocardial pathology) are incompletely understood. The disproportionate benefits of implementing biologic therapy in early disease are becoming increasingly apparent, raising the enticing possibility of transforming the natural progression of CVD co-morbidity, thereby reducing CVD risk and associated mortality. However, the effects of biologic treatment on CVD have not been studied in very early RA, where long-term benefits may be greatest.

5.3.2. Why this study is needed now: This study will address several of the current knowledge gaps listed above by quantifying CVD in patients with early RA and by studying the cardiovascular effects of early biologic therapy in this patient group. The study will use an MRI protocol that has been validated in other disease groups and pilot studies and has been translated to patients with established RA. Applying these methods to patients with early RA will provide novel insight into the mechanisms of CVD in RA and permit a detailed quantitative assessment of the effects of early biologic treatment.

5.3.3. Impact on disease burden: If this study can demonstrate beneficial cardiovascular effects of early biologic therapy for RA, it will make an additional strong argument for the appropriate wider use of such treatment in early RA especially those with poor prognostic markers.

5.3.4. Economic benefit: RA is associated with a significant health economic burden, mainly through the traditional consequences of the disease (i.e. joint pathology). CVD co-morbidity adds another notable dimension to the burden on the patient and NHS. Understanding the mechanisms of CVD in RA and the effect of treatment on CVD burden will be the first steps towards targeted therapies for patients with RA and long-term health-economic benefits.

5.3.5. Study context: Bolting on to the VEDERA trial will bring substantial economy to the proposal. Linking to the IACON registry subsequently will ensure long-term clinical follow-up of study patients.

5.3.6. Mechanisms of disease: By using a comprehensive MRI protocol that includes quantitative measurements of regional and global LV function, aortic stiffness, myocardial perfusion and extracellular myocardial volume fraction in a way that has not been undertaken before, this study will provide novel mechanistic insight into the pathophysiology of CVD in RA.

6. AIMS AND OBJECTIVES

6.1. Aims

The principle aim of this study is to provide guidance for rheumatologists and reassurance to the patient group whether early biologic treatment in patients with early RA can reduce CVD burden - the leading cause of mortality in RA patients and thus a central consideration in daily rheumatology practice. In exploratory analyses, we will evaluate whether in the future blood biomarkers may be substituted for the more expensive MRI scanning to estimate individual CVD burden. Furthermore, by linking the study to a long-term registry (IACON), we will generate clinical outcome data to inform future studies driven by clinical endpoints rather than surrogates.
Specifically, the following objectives will be addressed:

6.2. Objectives

6.2.1. Primary objectives:

- To determine if MRI can demonstrate cardiovascular abnormalities in a treatment-naïve inception RA cohort compared with controls.
- To establish whether anti-TNF therapy confers a quantitative difference in CVD as measured by MRI compared to standard therapy in a treatment-naïve inception RA cohort over a 12 month period.

6.2.2. Secondary objectives:

- To determine the proportions with pre-clinical CVD co-morbidity in a treatment-naïve inception RA cohort.
- To establish if any treatment effects of anti-TNF therapy are sustained over a 24 month period.

6.2.3. Exploratory objectives:

- To undertake (separately funded) bolt-on studies on biological samples (blood) collected from all patients recruited into the study to identify RA patients with a high-risk profile for pre-clinical CVD.
- To link MRI findings to clinical outcome through long-term follow up in the IACON registry (separately funded).

7. DESIGN

7.1. Overview

CADERA bolts on to the VEDERA trial, a prospective longitudinal intervention study of patients with early RA, randomized to either first-line anti-TNF therapy or optimal DMARD therapy. For the current proposal (CADERA), patients recruited to VEDERA will undergo cardiovascular MRI at baseline (prior to treatment) as well as after 1 year and 2 years of treatment. In order to determine that MRI can detect significant differences in CVD in the study cohort, 30 controls matched to the first 30 VEDERA patients will be recruited and MRI findings between the two groups compared. The change in CVD status as defined by MRI between baseline and follow-up in patients treated with early biologics or optimal DMARD therapy will be determined. At the end of the study all patients will enter the IACON registry.

7.2. VEDERA

VEDERA is an Investigator-Initiated Research (IIR) study funded by an unrestricted educational grant that is part of an IIR agreement with Pfizer. It is a phase IV, single-centre, randomised, study of 120 patients with early, treatment-naïve RA. The aim is to assess for the depth of remission (clinical and imaging) and immunological normalisation induced by immediate anti-TNF therapy (etanercept, ETN; subcutaneous, 50 mg weekly) and methotrexate (MTX) combination compared with initial MTX and a 'treat to target' regimen (optimal, standard, conventional therapy approach); with step-up in the latter group to ETN and MTX combination therapy in patients failing to achieve a pre-defined target after 24 weeks. All VEDERA patients consenting to CADERA will undergo cardiovascular MRI on a Philips 3T Achieva system based at Leeds General Infirmary.

7.3. CADERA

In parallel to the recruitment of VEDERA patients, a group of controls will be recruited, matched to study patients by

age and blood pressure, but with no history of RA. All recruited VEDERA patients will undergo baseline and 1 year and 2 year follow-up MRI scans. The primary endpoints are changes in MRI measurements at 1 year, with 2 year studies as exploratory endpoints.

8. ELIGIBILITY

The study population consists of 100 patients from the VEDERA study, who have recent onset RA and have not previously been treated with DMARD's. In addition, a control group of 30 patients without RA is recruited.

8.1. Inclusion Criteria

Patients: Males and females, aged between 18 and 80 years, diagnosed with RA according to 2010 ACR/EULAR criteria, who have not yet received therapy with disease modifying drugs, have early (symptoms for less than 1 year), active disease (clinical or imaging evidence of synovitis and DAS28- ESR >/= 3.2) and at least one poor prognostic factor (anti-citrullinated peptide antibody +/- abnormal power Doppler in at least 1 joint).
Controls: Males and females without RA, aged between 18 and 80 years, matched for age and blood pressure.

8.2. Exclusion Criteria

Patients: Previous treatment with DMARDs, contraindications to MRI and to anti-TNF therapy and severe co-morbidity that would in the clinician's opinion be associated with unacceptable risk of receiving potentially anti-TNF therapy, contraindications to MRI (incompatible metallic implants, pacemakers), renal failure (eGFR<30 ml/min/1.73m2), previous allergic reactions to MRI contrast agents, known CVD, contraindications to adenosine (asthma or high grade heart block).
Controls: History of RA or other inflammatory disease. Contraindications to MRI, contrast agents or adenosine or presence of renal failure as defined above. Known CVD.

8.3. Withdrawal criteria

Unwillingness or inability to complete the cardiovascular MRI study. Any side effects considered serious during the MRI scan.

9. RECRUITMENT PROCESS

9.1. Recruitment strategy

Patients will be recruited from the Leeds Teaching Hospitals Rheumatology service. The rheumatology group has a world-renowned established early arthritis referral system and dedicated clinic from which patients can be recruited. The group has the largest clinical trial participation in the UK and an audit in 2010-2011 confirmed almost 100 new cases of early RA in under 12 months. The recruitment period for VEDERA is expected to last up to 24 months and we have built our study time line to accommodate this (refer to Gantt). The rheumatology's portfolio in this area is based on an excellent track record of attracting industrial trials of biologics with over 250 trials of investigational medicinal products conducted over the past 15 years, with more than half academically sponsored [including a recent study ('IDEA') evaluating first-line anti-TNF versus MTX and steroid in 112 patients]. This has enabled access to study drugs and the ability to capitalise with novel experimental science like that being undertaken with CADERA. Whilst we have planned to recruit all CADERA subjects from VEDERA, as a contingency plan we will have the option to recruit from planned subsequent biologic studies with the relevant criteria for CADERA remaining unchanged from those detailed in section 5.1.

9.2. Subject Attrition

Recruiting from VEDERA has many advantages including the fact that the patients are already pre-screened for their eligibility to undergo MRI scanning. As a consequence we anticipate that uptake will be high and as the study provides early access to what patients regard as a desirable treatment therapy we anticipate few losses to follow up (please refer to Study Flowchart Section 19).

9.3. Resources

CADERA has been purposefully designed to bolt onto the separately funded VEDERA trial, reducing the study costs for this study considerably. VEDERA is funded with £1.194.758 and the treatment costs, safety visits and safety

monitoring are covered from this source. In the bolt-on CADERA study, we therefore mainly request support for staff to deliver this study, for cardiovascular MRI scanning and data processing/analysis.

9.4. Potentially Competing Studies

VEDERA and ACCUARCY are single centre studies the Division of Rheumatic & MSK Disease undertakes its flagship early arthritis strategically with no competing in-house studies. Both teams can therefore regulate the impact of competing studies so this is not an issue.

10. TREATMENT PATHWAYS/INVESTIGATION DETAILS

All recruited patients are randomised according to the VEDERA protocol into two groups: Experimental Treatment Arm - ETN group: immediate ETN and MTX treatment. Control Treatment Arm - Standard treatment group: initial MTX monotherapy with Treat to Target (TT) regimen: escalation to combination DMARD therapy at or after 8 weeks if failing to meet pre-defined target and step-up to ETN and MTX at 24 weeks if failing to meet pre-defined target of remission according.

10. OUTCOME MEASURES

The main outcome measures in this study are quantitative MRI measurements. Longitudinal changes of outcome measures in response to therapy will be measured and compared between the two treatment arms. Differences in outcome measures between the patient and control groups will be established.

10.1. Primary outcome measure

- Aortic distensibility

10.2. Secondary outcome measures

- Myocardial perfusion reserve
- LV strain and twist
- LV ejection fraction

10.3. Exploratory outcome measures

- Extracellular volume fraction from first pass perfusion and T1-mapping
- Biomarkers of CVD

10.4. Justification of the choice of outcome measures: Our pilot data suggest abnormalities in patients with RA in several quantitative MRI parameters including aortic distensibility, myocardial blood flow and global strain (although not all reached statistical levels in the small sample size). Among these, aortic distensibility showed the highest reproducibility. It has previously been shown (with other imaging modalities) that aortic distensibility relates to clinical outcome and that TNF alpha blockade improves aortic distensibility (see section 2.1.2.1.). We will therefore use this measurement as the primary endpoint in CADERA. MBF is a sensitive marker of both microvascular and macrovascular CVD. Previous PET studies and our pilot work have shown that RA leads to reduced MBF reserve (Recio-Mayoral 2009). PET studies in other conditions suggest that such changes can be reversible with therapy. We therefore expect MBF to be a highly sensitive and clinically relevant measurement in this study, but because of the lack of current evidence of reversibility of MBF abnormalities with treatment, we are using it as the main secondary endpoint in CADERA. LV mass and function by MRI will be additional secondary outcome measures to verify previous reports of previous smaller MRI studies, although we do not expect significant abnormalities in patients with early RA. In addition, strain and LV twist will be measured, reflecting earlier contractile abnormalities, which are more likely to demonstrate abnormalities in early RA. T1 mapping with calculation of the extracellular volume fraction is a relatively novel marker of CVD but may offer unique mechanistic insight into the underlying processes leading to myocardial disease in RA. We pioneered T1 mapping in Leeds almost a decade ago and are developing a database of normal and pathological data from other patient groups (BHF Senior Fellowship S Plein). We have also recently proposed methods to calculate microvascular blood volume from first pass perfusion (Broadbent 2012) and found abnormalities in patients with diabetes mellitus (unpublished). ECV may not be abnormal in early RA, but is a rapidly evolving measure and is therefore included as an exploratory outcome measure. Blood biomarkers complete the

exploratory analyses. It is anticipated that a phenotype at higher risk of CVD as defined by MRI can be indentified from biomarkers to provide a more cost-effective future screening tool.

10.5. MRI protocol: Cardiovascular MRI will be performed on a new dedicated cardiovascular 3 Tesla Philips Achieva system equipped with a 32 channel coil and Multitransmit technology that is located at Leeds General Infirmary but is owned by the University of Leeds. The MRI protocol tested in the pilot phase will be as follows: 1.Scout images to determine left ventricular short axis. 2. Baseline T1 mapping (ECG-triggered "Look Locker" inversion-prepared T1 weighted FFE-EPI, voxel size 1.5x1.5x8mm³, 16 phases, phase interval 100ms, 2 signal averages). 3. Adenosine stress first pass myocardial perfusion imaging (spoiled Turbo Gradient Echo, 5x k-t SENSE, 11 training profiles, 1.0x1.0x8mm³ spatial resolution, acquisition shot 110ms/slice, three short axis slices (Plein 2008), reconstructed with k-t PCA to improve temporal fidelity according to Pedersen (2009)). Adenosine at 140mcg/kg/min for 3 minutes. Perfusion data acquired over 5 minutes (for ECV measurement). 4. Cine images covering the entire heart in the LV short axis plane (balanced SSFP, spatial resolution 1.2x1.2x10mm³, 50 cardiac phases) and in orthogonal long-axis planes. 5. Tagged cine images with a three-dimensional CSPAMM method according to (Rutz 2008) 6. Aortic distensibility: two cine and phase velocity encoded images in the ascending aorta at the level of the PA bifurcation and in the descending aorta according to (Lee 2007). 7. First pass myocardial perfusion imaging at rest (as above). 8. Late gadolinium enhancement (inversion recovery gradient-echo) in a three-dimensional stack. In the pilot phase this protocol was completed in 64 (+/- 9) minutes. 9. Post contrast T1 mapping 15 minutes following last contrast injection (as above). Blood tests for haematocrit and renal function will be taken at the time of MRI scanning as required for measurement of ECV.

10.6. MRI analysis: From MRI data, the following quantitative measurements will be obtained: 1. LV and RV volumes and ejection fraction, LV mass and regional thickening, longitudinal LV shortening (MASS, Medis, Leiden, The Netherlands). 2. Resting MBF, hyperaemic MBF and MBF reserve (hyperaemic MBF / resting MBF) with Fermi-constrained deconvolution for subendocardial, mid-myocardial and subepicardial layers. 3. Measurement of microvascular and myocardial blood volume and myocardial capillary recruitment according to (Broadbent 2012). 4. Mean transmural MBF gradient using the "gradient-o-gram" method (Houtvast 2012). 5. Myocardial T1 values with a 3-parameter exponential fit with Look-Locker correction (www.osirix-viewer.com) and calculation of ECV according to (Flett 2012). 6. Strain and strain rate and twist/untwist/torsion from tagged CMR data (TagTrack software). 7. Aortic distensibility according to (Lee 2007).

10.7. Biomarkers: (please note that the Biomarker collection in the VEDERA-CADERA study is not requested from EME funding and has been secured from on-going studies in Leeds LMBRU). CADERA will enable linkage of biomarkers to MRI measurements of CVD. Specifically the following will be clinically evaluated: Rheumatoid factor anti-citrullinated peptide antibody, CRP, ESR, lipid profile, high-sensitivity CRP, serum amyloid A, fibrinogen, adiponectin, IL-6, TNF, intercellular adhesion molecule-1, vascular cellular adhesion molecule 1, CD40 ligand and NT-pro BNP.

11. ASSESSMENTS/SAMPLES/DATA COLLECTION

11.1. Assessment of efficacy/effectiveness

The main assessment of efficacy will be made from changes in the outcome measures between baseline and follow-up MRI to evaluate the study objectives. Clinical efficacy will be defined as a statistically significant improvement in the outcome measures. Comparison will be made between early RA patients either receiving a biologic versus standard DMARD TT approach. In addition, comparison of endpoints between the RA patient and a non-RA control group will be made.

As part of VEDERA, patients will be assessed at baseline and months 3, 6, 9, 12, 18 and 24. Patients in the 'control' arm will have monthly clinical assessment in the first 6 months to evaluate level of disease activity and escalate therapy as indicated (and in line with the ‚Treat to target' approach). In both arms additional visits outside of the study schedule may be included if clinically indicated.

11.2. Assessment of safety

There are very few safety concerns relating to the investigations in this study. Any complications arising during MRI

scanning will be recorded and assessed by the SCC. In the VEDERA Trial, formal Adverse Event (AE) and Serious Adverse Event (SAE) recording and reporting will be performed. Determination of AEs will be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the subject. AEs and SAEs will be collected from the signing of the informed consent form to 30 days after the end of a patient's participation in the trial (the last study visit at week 96 or early discontinuation visit). The investigator will instruct the subject to report AEs and SAEs during this time period. The investigator will follow up on all AEs and SAEs until the events have subsided, returned to baseline, or, in case of permanent impairment, until the condition has stabilized. Any unanticipated risks to the subjects must be reported promptly to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). The sponsor will maintain detailed records of all AEs and SAEs reported by an investigator in accordance with good clinical practice and applicable local regulations including, but not limited to, regulations implementing the requirements of Directive 2001/20/EC.

11.3 Definition of end of trial

The end of the trial is defined as the date of the last participant's last data item.

12. SERIOUS ADVERSE EVENTS PROCEDURES

12.1. GENERAL DEFINITIONS

An **adverse event** (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in the clinical study. The event does not need to be causally related to the test article or the clinical study. An AE includes, but is not limited to, the following:

- Any clinically significant worsening of a pre-existing condition.
- An AE occurring from overdose of a test article, whether accidental or intentional.
- An AE occurring from abuse (e.g. use for nonclinical reasons) of a test article.
    - An AE that has been associated with the discontinuation of the use of a test article.
    - For reports from post-marketing studies, any failure of expected pharmacologic action of a test article. For over-the-counter products, the recommended daily dose must be administered before failure of expected pharmacologic action can be attributed.

A **serious adverse event** (SAE) is an AE that:

- _Results in death.
- _Is life-threatening (see below).
- _Requires inpatient hospitalization or prolongation of an existing hospitalization (see below).
- _Results in a persistent or significant disability or incapacity (see below).
- _Results in a congenital anomaly or birth defect.
    - _Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do

Life-threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience that, had it occurred in a more severe form, might have caused death, but as it actually occurred did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life threatening, although angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalisation is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes a criterion for an AE to be serious; however, it is not in itself considered an SAE. In the absence of an AE, a

hospitalization or prolongation of a hospitalization should not be reported as an SAE by the participating investigator, but should still be recorded, in the following situations:

- _The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.
- _The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the centre (e.g. stent removal after surgery).
- _A hospitalization for a pre-existing condition that has not worsened.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions. If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

A **protocol-related adverse event** is an AE occurring during a clinical study that is not related to the test article but is considered by the investigator or the medical monitor (or designee) to be related to the research conditions, i.e. related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

A **Suspected Unexpected Serious Adverse Reaction** (SUSAR) is a serious adverse event suspected to have a reasonable causal relationship to the investigational medicinal product where the nature or severity of the reaction is inconsistent with the available product information (mainly referring to the Summary Product Characteristic Brochure).

Other Reportable Information. Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes the following:

- _Pregnancy exposure to a test article, except for exposure to prenatal vitamins. If a pregnancy is confirmed, use of the test article must be discontinued immediately. Information about the pregnancy exposure includes events over the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings. Both maternal and paternal exposures are considered other reportable information. For exposure involving the female partner of a male subject, the necessary information must be collected from the subject, while respecting the confidentiality of the partner.
- _Lactation exposure to a test article, with or without an AE.
- _Overdose of a test article as specified in this protocol, with or without an AE. Baby formula overdoses without any AEs are excluded.
- _Inadvertent or accidental exposure to a test article, with or without an AE.

12.2. Efficacy Endpoints and Disease Progression Events

All events that are unequivocally due to progression of moderate to severe rheumatoid arthritis or lack of response should not be reported as an AE or SAE. This type of information will be captured in the study assessments. Disease progression would include: increased joint pain, musculoskeletal pain, generalized body aches, uncontrolled RA, joint swelling, increased stiffness, limited motion, synoviorthesis (in or out of the hospital), and hospitalizations for RA-related procedures (joint replacement surgery, joint arthroscopy, synovectomy).

12.3. Adverse Event and Serious Adverse Event Recording and Reporting

Determination of AEs should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the subject. In addition to the information obtained from these sources, the subject should be asked a nonspecific question such as: "How have you been feeling since your last visit?" Signs and symptoms must be recorded using standard medical terminology. Subjects considered incapable of giving consent would not be considered for this study. AEs and SAEs will be collected from the signing of the informed consent form to 30 days after the end of a patient's participation in the trial (the last study visit at week 96 or early discontinuation visit). The investigator must instruct the subject to report AEs and SAEs during this time period.

During the time period specified above, the investigator will:

- Record all AEs and SAEs on source documents.
- Record all AEs and SAEs in the study records for subjects who are not screen failures.
- Report all SAEs on a 'Serious Adverse Event/Expedited Report from a Clinical Trial'. Instructions on where to send this form will be provided by the sponsor.

The investigator must follow up on all AEs and SAEs until the events have subsided, returned to baseline, or, in case of permanent impairment, until the condition has stabilized. Any unanticipated risks to the subjects must be reported promptly to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). The sponsor will maintain detailed records of all AEs and SAEs reported by an investigator in accordance with good clinical practice and applicable local regulations including, but not limited to, regulations implementing the requirements of Directive 2001/20/EC.

12.4. Serious Adverse Event and SUSAR Reporting Requirements

All SAEs, other information reportable as SAEs and follow-up information must be reported to the sponsor within 24 hours (1 business day) of the research team becoming aware of them, by faxing a completed SAE form 'Serious Adverse Event/Expedited Report from a Clinical Trial' to the fax number 0113 392 6397 (the number provided by the sponsor). The sponsor will confirm, by phone or e-mail, that the fax was received. A business day is defined as any day except weekends, and United Kingdom bank holidays. Suspected adverse reactions that are both serious and unexpected are subject to expedited reporting in accordance with all applicable global laws and regulations. In the European Economic Area (EEA), the sponsor will ensure reporting of suspected unexpected serious adverse drug reactions (SUSARs), for the investigational medicinal product(s) used in the clinical study to the IECs and competent authorities of the EEA Member States where the study is being conducted. SUSARs will be reported in accordance with the requirements and provisions of Directive 2001/20/EC and relevant implementation guidelines, and as transposed into the applicable national laws. They will all be signed off by the principle investigator or, in their absence, by a delegated individual.

15. ENDPOINTS

The main outcome measures in this study are quantitative MRI measurements. Longitudinal changes of outcome measures in response to therapy will be measured and compared between the two treatment arms. Differences in outcome measures between the patient and control groups will be established.

15.1. Primary outcome measure

- Aortic distensibility

15.2. Secondary outcome measures

- Myocardial perfusion reserve
- LV strain and twist
- LV ejection fraction

15.3. Exploratory outcome measures

- Extracellular volume fraction from first pass perfusion and T1-mapping
- Biomarkers of CVD

16. STATISTICAL CONSIDERATIONS

Powering is based on scaling of effect sizes reported by Ikonomidis et al. (2008). We have contacted the author and obtained confirmation of the data they presented. Our effect size of 2.46 cm^2 $dyne^{-1}10^{-6}$ represents the smallest

detectable difference above measurement error. We propose 2.46 as an effect size in our power calculation (representing 75% of the difference between treated and non-treated RA patients reported by Ikonomidis et al., 2008). Assuming a SD of 3.5, 5% significance level in a two-tailed independent samples t-test at 90% power, 50 patients would be required per group - biologic therapy versus standard conventional therapy - (adjusting for 10% drop-out). For comparison with controls, we will directly match RA versus non-RA patients on age and blood pressure categories as the two principal factors influencing aortic distensibility (study primary end-point). Exploratory analysis for imbalance between case/control groups on other covariates potentially influencing distensibility (such as gender, hyperlipidaemia, diabetes and smoking) will be conducted (Dart 2001; Resnick 1997; Rogers 2001; Simon 1985). If imbalance is identified as problematic, adjustments to the matching within a propensity scores framework (Ho et al., 2011) will then be made based on the additional covariates. Analysis will be conducted in the R environment for statistical computing (R Core Team, 2012) using paired t-tests or Wilcoxon signed-rank tests depending on the plausibility of normality assumptions. The Matchit R library will be used, if appropriate, for further propensity score matching prior to analysis. Based on reliability data in healthy controls, the smallest detectable difference above measurement error, based on the 95% limits of agreement, is $2.46 cm^2\ dyne^{-1} 10^{-6}$. Assuming the standard deviation (SD) of the measurements will be $3.5 cm^2\ dyne^{-1} 10^{-6}$ (based on data from the Anakinra RA treatment group in Ikonomidis et al., 2008), then at 5% significance (two-tailed), assuming a paired t-test, 27 patients per group would be required for 90% power (assuming 10% drop out). The seminal text of Lancaster et al. (2004) for pilot studies (where only limited data to perform power calculations are available) recommends a minimum sample size of 30 in each group. We will therefore recruit 30 cases and 30 controls.

17. STATISTICAL ANALYSIS

All statistical analysis will be conducted in the software package R (R Development Core Team, 2012).

Early anti-TNF RA treated and conventional RA treated patients will be compared with primary outcome aorta distensibility at 1 year follow up and secondary outcome change in blood flow reserve at baseline to 1 year. The objective is to determine if a significant difference ($p<0.05$) between treated and non-treated groups exists and to estimate the magnitude of this difference as a 95% confidence interval. Exploratory Data Analysis will be used to determine if parametric (independent samples t-test) or non-parametric (Wilcoxon rank sum test) analyses are appropriate and to summarise the distribution of aorta distensibility and change in blood flow reserve across RA treated and RA non-treated patients. These analyses will also allow the credibility of an equal variance assumption to be assessed in parametric modelling, and appropriately modelled (Cressie 1986). All patients meeting eligibility criteria will be included in the analyses and these will be conducted at the end of the recruitment period. Exploratory sub-group analyses will be conducted separately by other comorbidities, maximum of 2-3 that are clinically plausible, with appropriate correction for multiple testing (Benjamini 1995). Interactions between subgroups and interactions between MRI findings and biomarkers and will be explored through building a linear model with interaction terms (Fox 2008). Patterns of CVD pathology in RA patients will be described. Treatment effects on secondary outcome measures and effects at the 2 year follow-up point will analysed in an equivalent manner.

RA versus non-RA patients will be compared with primary outcome aorta distensibility and secondary outcome blood flow reserve using matched paired analysis. The objective is to determine if a significant difference ($p<0.05$) between RA and non-RA patients exists, and to estimate the magnitude of this difference as a 95% confidence interval. Exploratory Data Analysis will be used to determine if parametric (paired samples t-test) or non-parametric (Wilcoxon matched pairs test) analyses are appropriate and to summarise the distributions of aorta distensibility and blood flow reserve across RA and non-RA patients. All patients meeting eligibility criteria will be included in the analyses and these will be conducted at the end of the recruitment period.

18. DATA MONITORING

18.1. CADERA

The University of Leeds, which is the host institution of Plein will sponsor the study. The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the Department of Health Research Governance Framework for Health and Social Care, 2005. The study will not be initiated before it has obtained approvals from the respective IRAS and National Health Service (NHS) Research & Development (R&D) departments.
In order to ensure cost effectiveness, CADERA study management will be closely linked to the VEDERA trial. The VEDERA Trial Steering Committee will provide oversight to CADERA. An additional CV expert will be joining the VEDERA TSC for this purpose. We will follow the sponsor's proposed time period for retention of relevant anonymised clinical data of 15 years following the end of a study (according to the MRC guidelines). The University of Leeds will archive all paper and electronic records in a legacy format according to GCP requirements.

18.2. VEDERA

The University of Leeds is the study sponsor. The CADERA SMG and SSC will work in close collaboration with the equivalent VEDERA committees. The VEDERA Trial Steering Committee (TSC) has independent oversight of the study and amongst its members are an independent chair (Prof. G. Wilson), a lay individual (from the Leeds Musculoskeletal Biomedical Research Unit Public and Patient Advocacy Group), Buch (study PI) and Anne-Maree Keenan (Divisional Research and Development Lead). The group has agreed to meet annually. No Monitoring or Data Collection will be undertaken by Pfizer. Under the Development Safety Update Report (DSUR) Guidance (ICH E2F) the sponsor will submit an annual safety report to the MHRA and the Ethics Committee throughout the clinical trial or on request. The annual safety report will take into account all new available safety information received during the reporting period. Direct access to the on-site study documentation and medical records will be ensured. Refer to Section 9 for further measures of safety monitoring.

19. QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

19.1 QUALITY ASSURANCE

The study will be conducted in accordance with the principles of Good Clinical Practice in clinical trials as detailed by the Medical Research Council (1998), the NHS Research Governance Framework (*and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006 for studies conducted in Scotland)* and through adherence to CTRU Standard Operating Procedures (SOPs).

19.2 ETHICAL CONSIDERATIONS

Ethical approval (IRAS) and R&D approvals to add cardiovascular MRI studies to the VEDERA protocol have been obtained. Information will be provided verbally and through an information sheet, developed in consultation with patients and Liz Carrington and Ailsa Bosworth our PPI representatives. We have the option to also draw upon other local patient involvement groups from both LMBRU and a CVD Patient Group as required). The information sheet clearly explain the participation in the CADERA study is voluntary with the option of withdrawing from the study at any stage, and that participation or non-participation will not affect their usual care. Only individuals who are NHS employees (substantive or honorary) and who have access permissions will examine hospital databases for potentially eligible participants. Only patients providing informed consent will take part in CADERA. Any incidental findings on MRI scanning will be reported to the patient's GP.

20. CONFIDENTIALITY

Only the subject number and subject initials will be recorded in the case report form, and if the subject name appears on any other document (e.g. laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor, independent ethics committee (IEC)/

institutional review board (IRB), or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.
The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

20.1 ARCHIVING
Essential documents will be retained for 15 years after the end of the trial. However, because of international regulatory requirements, the sponsor may request retention for a longer period.
Essential documents include:

- Signed informed consent documents for all subjects.
- Subject identification code list (European Union legislation requires this list to be maintained for a minimum of 15 years), screening log (if applicable) and enrolment log.
- Record of all communications between the investigator, the REC and the sponsor.
- Composition of the REC, and the sponsor (or other applicable statement as described in section 24.6).
- List of sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant trial-related duties, together with their roles in the study and their signatures.
- Copies of case report forms and documentation of corrections for all subjects.
- Investigational product accountability records.
- Record of any body fluids or tissue samples retained.
- All other source documents (subject medical records, hospital records, laboratory records, etc.).
- All other documents as listed in section 8 of the ICH E6 Guideline for Good Clinical Practice (Essential Documents for the Conduct of a Clinical Trial).

Normally, these records will be held in the investigator's archives. If the investigator is unable to meet this obligation, he or she must ask the sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

21. STATEMENT OF INDEMNITY

Indemnity to meet the potential legal liability of the researchers is provided through the NHS indemnity scheme.
The sponsor has insurance to cover any negligence on its behalf (in the design of the research).
Further details of liability and insurance provisions for this study are given in separate agreements.

22. STUDY ORGANISATIONAL STRUCTURE

22.1 INIDIVUALS AND INDIVIDUAL ORGANISATIONS

Trial Sponsor – The Sponsor is responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC.

Chief Investigator: The Chief Investigator will have overall responsibility for the design, set-up and implementation of the study.

Clinical Research Nurse (CRN): The CRNs will be responsible for patient recruitment, obtaining informed consent, randomisation, liaison with medical staff, CRF completion and annual follow-up assessments (including GP contact, patient telephone follow-up and case-note verification).

CADERA Research Fellow: The Research Fellow will be responsible for the medical supervision of CMR imaging, the CMR analysis, day-to-day clinical input into the study and supporting the CRN in patient recruitment.

CADERA medical physicist: The physicist will be responsible for pulse sequence optimisation and implementation at recruiting sites, quality control assessments, phantom calibration work, and image quality/artefact problem solving.

Funding: The study is funded by an EME 5 year Grant.

22.2 GROUPS

Trial Management Group - The TMG, comprising the Chief Investigator, co-applicants, trial manager, PPI representative and CADERA research fellow will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation and publishing of the results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the main REC and supporting applications for Site Specific Assessments, (iv) completing cost estimates and project initiation, (v) nominating members and facilitating the TSC and DMEC, (vi) reporting of serious adverse events, (vii) monitoring of screening, recruitment, treatment and follow-up procedures, (vii) auditing consent procedures, data collection, trial end-point validation and database development. The TMG will meet three-monthly.

Trial Steering Committee – Independent oversight of the study will be conducted by the VEDERA Trial Steering Committee, with the addition of a cardiovascular disease expert. Amongst its members will be an independent chair, a lay individual (from the Leeds Musculoskeletal Biomedical Research Unit Public and Patient Advocacy Group), Professor Paul Emery (Head of the Section of Musculoskeletal Disease) and Anne-Maree Keenan (directorate Research and Development Lead), CV expert tbc.

Trial Steering Committee Terms of Reference

1. To monitor and supervise the progress of the trial "A Prospective, Single-centre, Randomised Study Evaluating the Clinical, Imaging and Immunological Depth of Remission Achieved by Very Early versus Delayed Etanercept in patients with Rheumatoid Arthritis (VEDERA)" towards its interim and overall objectives
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 and Ethics Committee
4. In the light of 1,2 and 3, to inform the Sponsor (the University of Leeds), the Funding organisation and relevant organisations on the progress of the trial

Specifically, the Trial Steering Committee will be responsible for monitoring the following (See MRC Guidelines for Good Clinical Practice in Clinical Trials 1998 document)

- Patient safety
- Progress of the Trial
- Adherence to Protocol
- Consideration of New Information

22.3 MONITORING

Monitoring and audit will be carried out by persons approved by the sponsor to assess quality of patient care and data; this includes the research team. Monitoring and auditing procedures developed or endorsed by the sponsor will be followed, in order to comply with GCP guidelines. Direct access to the on-site study documentation and medical records must be ensured. Patient consent will be obtained for this in the informed consent form.

22.4 SOURCE DATA VERIFICATION AND PROTOCOL COMPLIANCE

Data Verification and Protocol Compliance will be done by the investigators and members of the study team who will check the case report forms for completeness and clarity, and crosscheck them with source documents.

22.5 ON-SITE AUDITS: QUALITY ASSURANCE

The sponsor has systems in place to ensure that there is reporting and appropriate action taken in respect of:

- Serious breaches of GCP, the trial protocol and the Clinical Trial Authorisation.
- Urgent safety measures
- Protocol violations

A "serious breach" is a breach which is likely to effect to a significant degree either:

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial.

Investigators will promptly notify the Sponsor Quality Assurance Office of the following within the required timeframe, once they become aware of:

- Serious breaches of GCP, the trial protocol and the Clinical Trial Authorisation will be reported within 24 hours (1 business day) from the time the research team becomes aware of the incident.
- Urgent safety measures
- Protocol violations
- Any amendments to the trial
- Any changes the Clinical Trial Risk Assessment (form A).
- Any other issues as stated in the Research Sponsorship Agreement (RSA)

The Sponsor reserves the right to audit any site involved in the trial and authorisation for this is given via the Research Sponsorship Agreement (RSA).

23. PUBLICATION POLICY

The trial will be registered with an authorised registry, according to the ICMJE Guidelines, prior the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- and final approval of the version to be published
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator, co-applicants and relevant senior and statistical advisors will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial. The CADERA team should be acknowledged in all publications, as should the NIHR/EME. Other key individuals will be included as authors or contributors as appropriate and at the discretion of the CADERA TMG. Any disputes relating to authorship will be resolved by the TSC.

The Chairs and Independent members of the TSC and Data Monitoring and Ethics Committee (DMEC) will be acknowledged, but will not qualify for full authorship, in order to maintain their independence.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.'

The NIHR/EME (funder) has adopted an open access policy for all NIHR funded research which means that an electronic copy of all peer reviewed published papers must be accessible via the UKPMC website.

24. REFERENCES

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Appendix 1: PATIENT INFORMATION SHEET and CONSENT FORM

The Leeds Teaching Hospitals NHS
NHS Trust

A Prospective, Single-centre, Randomised Study Evaluating the Clinical, Imaging and Immunological Depth of Remission Achieved by Very Early versus Delayed Etanercept in patients with Rheumatoid Arthritis (VEDERA)

CARDIOVASCULAR SUB-STUDY

Subject ID: Initials _____ DOB _____

You are being invited to take part in a clinical research study. The main part of this study is described in a separate information sheet which your doctor should provide you with. There is a smaller part of the study (a sub-study) which involves collecting some extra information from you and is discussed below. It is not necessary to take part in this sub-study.

The drug treatments used in this study are not experimental; they are currently used to treat rheumatoid arthritis. Leeds Teaching Hospitals Trust and the University of Leeds are conducting a research study to gather more information about using these treatments.

Before you decide on participating, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives or your GP if you wish. Ask us if there is anything that is not clear or if you would like some more information. We want to be sure that you understand what the study is about.

General information on clinical trial participation can be found on the website of the National Electronic Library for Health (http://www.library.nhs.uk/trials). A paper copy of the information available on this website can be obtained from your study Doctor or Nurse.

Please take time to decide whether or not you wish to take part in this study. You may decide to take part in the main study, but not in this smaller sub-study. Thank you for reading this.

1. WHAT IS THE PURPOSE OF THIS SUB-STUDY?

As well as measuring the effects of treatment, including the effect of the drug etanercept, on arthritis we aim to look at the effect it has on the heart and blood vessels. This is important because, in long-standing rheumatoid arthritis, there is an increased risk of heart disease and disorders of blood vessels, such as stroke.
In addition to the main study you will be asked to undergo:

- Extra blood tests. Up to 20 mls (approximately 2 tablespoons) of extra blood will be taken at three of the study visits. This will be tested in this substudy, but it will also stored (in an anonymised way, i.e. your identity will not be shown on the samples) for possible future research.
- Pulse Wave Velocity measurements. This measures how fast blood travels from one point in the body to the next. Blood travels faster if blood vessels are stiffer, and stiffer blood vessels suggest a higher risk of cardiovascular disease.
- Magnetic Resonance Imaging (MRI) of the heart. MRI is a widely used and safe technique for imaging soft tissues within the body. MRI can assess what the blood vessels look like and how well the heart functions.

2. WHY HAVE I BEEN CHOSEN?
You are being asked to take part in this research study because you have been recently diagnosed with rheumatoid arthritis and you have been asked to take part in the main study. Your arthritis is active but you have not yet started taking any DMARDs such as methotrexate to control it. You are therefore suitable for early etanercept treatment.

It is expected that 120 patients will take part in this study within the UK.

3. DO I HAVE TO TAKE PART?
No. It is up to you to decide whether or not to take part. You can decide to take part in only the Main Study, and not this Cardiovascular Sub-study. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive and your doctor will discuss other treatment options with you.

4. WHAT WILL HAPPEN TO ME IF I TAKE PART?
All the participants will receive the treatment as detailed in the Main study patient information sheet (your Doctor or Nurse should provide you with this). However, if you agree to take part in the Cardiovascular sub-study you will also receive extra blood tests, pulse wave velocity measurements and a heart MRI scan at baseline (the start of the study), the 48 week (12 month) visit, and the 96 week (2 year) visit.

- Extra blood tests. Up to 2 tablespoons of extra blood will be collected. The blood tests require that you are in a fasted state, and so we ask you not to drink or eat anything for 8 hours before your test. The blood tests will be done in the morning to make this easier for you. This blood (including DNA, genetic information) will be stored and used solely for future laboratory based research.
- Pulse wave velocity measurement takes about 15 minutes. You will be asked to lie down on an examination couch. Two small pads will be placed on your skin at a set distance apart, one on the neck, the other at the top of the thigh, and the speed at which the blood flows will be measured. This involves no needles and is non-invasive. You will not be required to remove any items of clothing.
- The MRI scans take about 60 minutes and will be performed at Leeds General Infirmary. You lie in a short 'tunnel', which holds a large magnet. Short bursts of radio waves from the MRI scanner allow images to be created. You will hear periodical loud “banging” noises while we are acquiring the images, but we protect your ears with headphones through which you can listen to the radio or one of your own CDs. We will remain in communication with you throughout the scan. If you have normal kidney function then once during the heart scan, we will inject an MRI contrast medication into a vein in your arm. The needle used for this will feel like a sharp scratch. Usually people are not aware of the contrast dye injection. Should your kidneys be impaired then the injection will not be given. Another injection (of a medication called Adenosine) may be given which makes the heart pump a little faster to see what the heart is like under stress. Adenosine can cause a brief feeling of warmth, breathlessness or chest discomfort. However all of these feelings, if they occur, usually settle within one or two minutes. You will be asked to fast for 6 hours prior to each scan and not drink tea, coffee, other caffeinated drinks or alcohol for 24 hours before each scan.

5. WHAT IF I DO NOT WISH TO TAKE PART?
All studies are always completely voluntary. If you do not wish to take part in this sub-study this will not affect the main study. If you do not wish to take part in either this sub-study or the main study this will not affect the treatment you will receive in clinic.
If you decide to take part, you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

You should be aware that if in the future you experience the loss of capacity (i.e. ability to agree to continue to take part in the study), the research team would retain tissue and personal data collected and continue to use it confidentially. This could include further research after the current project has ended.

6. WHAT DO I HAVE TO DO?

It is very important that you strictly follow the study procedures and all your doctor's recommendations and prescriptions during the study. Any change in your health (such as signs or symptoms, doctor visits, hospitalisations, laboratory tests) or change in your medications should be reported to your doctor or to the study nurse. If you become pregnant, you must report this to the study doctor immediately. We will notify your GP of your participation in the study, unless you instruct us not to.
There are frequent clinic visits to attend throughout the study, however, you are able to continue your normal diet, driving and leading an active life as you had prior to joining this study. You will be provided with a study card, which you should keep with you during the course of the study, with details of how to contact your doctor or other study related personnel.

7. WHAT IS THE TREATMENT BEING TESTED?

This is a research study of drug called "etanercept". It was approved for use in RA in 1998. More than half a million patients have received etanercept around the world. Because it is expensive, its use is restricted in some healthcare systems, including the NHS, to the most severe patients who have failed other treatment. This study will evaluate use of etanercept at the start of disease to see if it leads to larger benefits.

Etanercept is a protein called a TNF-inhibitor. It blocks the action of TNF (tumour necrosis factor) which causes inflammation. By reducing inflammation in joints it reduces the symptoms of RA and protects the joints from damage.

8. WHAT ARE THE ALTERNATIVES FOR TREATMENT?

Alternatives to participating in this study include treatment with standard DMARDs including methotrexate, sulfasalazine and hydroxychloroquine. If you choose not to take part in this study, etanercept and other therapies may be available to you in the future if you do not respond to treatment with two DMARDs. More information is available from your doctor on the risks and benefits of taking these drugs. You should discuss other treatment options with your doctor, so that you have enough information to decide if you want to join this study.

9. WHAT ARE THE RISKS OR SIDE EFFECTS OF TAKING PART?

For side effects and risks involved with the study treatments please refer to the main study information sheet. The side effects or discomfort you may experience specific to this sub-study are:

- Collection of blood may cause symptoms such as local pain, bleeding, bruising, fainting, and rarely infection.
- Magnetic Resonance Imaging (MRI) is safe and no radiation is used for this scan. There are no known risks from this technique. Some people may experience claustrophobia. Our MRI staff will do all that they can to make you feel comfortable during the scan, and will be monitoring you via a video camera and an audio link. If we are unable to make you feel comfortable in the scanner, we will not go ahead with scanning. The contrast medication which we use is very safe but, as with any injection, reactions may occur. These include a warm sensation at the injection site, nausea or vomiting and transient skin rash. These effects usually only last for a few minutes. People with a history of allergy are more likely to suffer a more severe reaction, but this is rare (less than 1 in 3000). The department is equipped to cope with allergic reactions if they happen and medical staff will be on hand to deal with

any unforeseen circumstances or problems. Adenosine, the medication we use to increase the blood flow to the heart, can cause flushing, breathlessness and chest discomfort. However, all of these feelings usually subside within one or two minutes or even more quickly if the medication is stopped

10. WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?
Beneficial information may be acquired for patients who develop rheumatoid arthritis and may help us to better treat patients in the future. No personal benefits will be gained directly for yourself.

11. WILL I RECEIVE FINANCIAL COMPENASATION FOR TAKING PART?
You will not receive any financial compensation for taking part in this study. You will be compensated for any reasonable travel costs associated with the study.

12. WHAT IF NEW INFORMATION BECOMES AVAILABLE DURING THE STUDY?
Sometimes during the course of a research study, new information or side effects become known about the treatment that is being studied. If this happens, your doctor will tell you about it, and discuss with you whether or not you want to continue in the study. If you decide to withdraw your doctor will arrange for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form. Also, on receiving new information your doctor might consider it to be in your best interests to withdraw you from the study. They will explain the reasons and arrange for your care to continue.

13. WHAT HAPPENS IF THE RESEARCH STUDY STOPS?
Occasionally during the course of a study the company sponsoring the research may stop it. If this happens in this study, your doctor will give you information on the alternative treatments for your rheumatoid arthritis. You will have the option to continue to have your routine follow-up visits at the Rheumatology Department at Chapel Allerton Hospital.

14. WHAT IF SOMETHING GOES WRONG?
If you develop a problem that requires medical attention, you should contact the Doctor immediately. You will then be given medical care and advice in the usual way. If taking part in the study harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action. Regardless of this, if you have cause to complain about any aspect of the way you have been approached or treated during this study, then normal National Health Service complaint mechanisms are available to you.

15. WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?
The information will be kept confidential and data will be stored according to the Data Protection Act using appropriate security. If you consent to taking part in the research, any of your medical records may be looked at by trial Sponsor, University of Leeds and regulatory authorities or their representatives to check that the study is being carried out correctly. Your name and address, however, will not be disclosed outside the hospital. A copy of your consent form will be sent to the Sponsor of this trial and kept securely on file within the Quality Assurance office.

16. WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY? The results from the study will be compiled on a database. Once every patient involved in the study has completed the study, the results will be analysed by statisticians. The study result will be written up in a final report, which will be given to your doctor. The result may also be published in a scientific journal and available to the wider medical community. However, you will not be identified in any report or publication.

Your blood samples will be stored within a planned secure BioBank and may be used for additional research activities. Researchers undertaking this additional research will not be able to identify you and all projects will be reviewed by a Research Ethics Committee.

17. WHO IS ORGANISING AND FUNDING THE RESEARCH?
This study is being organised and sponsored by the Department of Rheumatology at the University of Leeds. Your study doctor and nurse will receive no payment for doing this study. The study is being funded by the Department of Rheumatology and Pfizer (the company that makes etanercept). This study has been reviewed and approved by the Leeds West Research Ethics Committee.

18. CONTACT NAMES AND NUMBERS
If you need any further information, please do not hesitate to contact your study nurse or doctor.

Principal Study Investigator
Name: Dr. Maya H. Buch
Your Doctor
Name: Dr Sarah Horton Tel. Number: 0113 3924729

Your Research/Specialist Nurse
Name: David Pickles Tel. Number: 0113 3924960

Chapel Allerton Hospital
During working hours Tel. Number: 0113 3924729
Ward 8: 0113 3924798
After hours Ward 2: 0113 3924502

Alternatively if you or your relatives have any questions about this study you may wish to contact the following organisations that are independent of the hospital at which you are being treated: • Arthritis Research UK, 0300 790 0400, http://www.arthritisresearchuk.org

If you decide you would like to take part then please read and sign the consent form. You will be given a copy of this information sheet and the consent form to keep. A copy of the consent form will be filed in your patient notes, one will be filed with the study records and one may be sent to the Research Sponsor.

You can have more time to think this over if you are at all unsure.
Thank you for taking the time to read this information sheet and to consider this study

The Leeds Teaching Hospitals NHS
NHS Trust

Patient Consent Form: CARDIOVASCULAR SUBSTUDY

A Prospective, Single-centre, Randomised Study Evaluating the Clinical, Imaging and Immunological Depth of Remission Achieved by Very Early versus Delayed Etanercept in patients with Rheumatoid Arthritis (the VEDERA study)

Principle Investigator: Dr. Maya Buch

Patient Details: Subject Identification number: _____ DOB: _____ Initials: _____

Please initial on the line:

1. I have read version 7.0 dated 01/06/2012 of the patient information sheet for the above study. I have had the opportunity to ask questions about the study and to discuss it with family and friends. I have spoken to Dr and feel my questions have been answered. I understand the purpose of the study, and how I will be involved. _____

2. I understand that all information collected in the study will be held in confidence and that, if it is presented or published, all my personal details will be removed. _____

3. I give permission for responsible and authorised individuals from the Sponsor and regulatory authorities (research ethics committee) to have access to my medical notes where it's relevant to my taking part in the research (to ensure quality of the study), with the understanding that no personal details which might identify me will be presented or published without my permission. _____

4. I confirm that I will be taking part in this study of my own free will, and I understand that I am free to withdraw from the study at any time without giving a reason, affecting my future care or legal rights. _____

5. I agree for the blood samples from this study to be submitted to the Rheumatology department BioBank, where they will be stored in an anonymised way and may be used future research. _____

6. I am happy for you to contact my GP about my participation in this study. _____

7. I agree that a copy of my consent form can be sent to the Sponsor's office. _____

Signed _____ Date _____ Name (block capitals) _____
Patient

I have explained the study to the above named patient and he/she has indicated his/her willingness to participate.

Signed _____ Date _____ Name (block capitals) _____
Investigator

6/6