Supplementary File 1 STAPRA study protocol

Research Protocol

STAtins to Prevent Rheumatoid Arthritis (STAPRA)

Prevention of Rheumatoid Arthritis by Atorvastatin in Seropositive Arthralgia Patients: a Multicenter Double-Blind Randomized Placebo-Controlled Trial

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CONTENTS

1. GENERAL INTRODUCTION

Short title	STAtins to Prevent Rheumatoid Arthritis (STAPRA)		
Version and date of protocol amendments	Version 3 February , 2015		
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Medical condition or disease under investigation	Rheumatoid arthritis, seropositive arthralgia		
Trial design	Multicenter double-blind randomized placebo-controlled trial of atorvastatin in seropositive subjects with or without arthralgia		
Purpose of clinical trial	To determine whether the development of rheumatoid arthritis (RA) can be prevented or delayed by atorvastatin in persons at high risk for RA		

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Sample size	220 patients; 110 will be given atorvastatin, and 110 will receive placebo.
IMP, dosage and route of administration	Study subjects will be randomized 1:1 to receive oral atorvastatin 40 mg OD or placebo OD

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2. LIST OF ABBREVIATIONS

ABI	=	ankle brachial index
ACPA	=	anti-citrullinated protein antibodies
AE	=	adverse event
APO	=	apolipoprotein
ALAT	=	alanine transamidase
BMI	=	body mass index
cIMT	=	carotid intima media thickness
CD	=	cluster of differentiation
CK	=	creatine kinase
CRF	=	case record form
CRP	=	c-reactive protein
CV	=	cardiovascular
DAS-28	=	disease activity score in 28 joints
DM	=	diabetes mellitus
DMARDs	=	disease-modifying antirheumatic drugs
ECG	=	electrocardiogram
ESR	=	erythrocyte sedimentation rate
EQ5D	=	euroqol 5 dimensions
FDR	=	first degree relatives
GP	=	general practitioner
HAQ	=	health assessment questionnaire
HDL	=	high density lipoprotein
HMG-CoA	=	hydroxy-3-methylglutaryl-coenzyme A
IgM	=	immunoglobulin M
LDL	=	low density lipoprotein
METc	=	medical ethics research committee
OD	=	once daily
PWA	=	pulse wave analysis
PWV	=	pulse wave velocity
RA	=	rheumatoid arthritis
RCT	=	randomized clinical trial
RF	=	rheumatoid factor
RNA	=	ribonucleic acid

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SAE	=	serious adverse event
SBD	=	systolic blood pressure
SOC	=	system organ class
SPC	=	summary of product characteristics
SUSAR	=	suspected unexpected serious adverse reaction
TC =		total cholesterol
TG =		triglycerides
Th	=	T helper cell
TSH	=	thyroid stimulating hormone
ULN	=	upper limit of normal
UMCG	=	Universitair Medisch Centrum Groningen
VAS	=	Visual Analogue Score
VUmc	=	VU University Medical Center
WHR	=	waist-to-hip ratio
WMO	=	wet maatschappelijke ondersteuning

3. SUMMARY

Background and hypothesis

Rheumatoid arthritis (RA) affects the joints and can lead to serious disability. In RA, a preclinical phase is often present, in which patients do not have arthritis, but do exhibit specific antibodies, often accompanied by vague joint symptoms and general symptoms. The existence of an at-risk phase enables us to investigate interventions with the goal of preventing the development of RA.

One of the major complications of RA is cardiovascular (CV) disease, which is doubled in comparison to the general population. Inflammation is thought to play an important role in this increased risk. Dyslipidaemia is also present, many years before RA becomes clinically apparent.

Therefore, we hypothesize that statin therapy, due to its combined lipid-lowering and anti-inflammatory effects, may be able to prevent the development of clinical arthritis in persons at increased risk for RA.

Study objective

To investigate whether statin treatment can prevent or delay the development of clinical arthritis in persons at increased risk of RA.

Study population

Persons aged 18 years and older, who are either IgM-RF and ACPA positive or have a high ACPA titer (>3x ULN).

Study design

Multicenter double-blind randomized placebo-controlled trial.

Intervention

Atorvastatin 40 mg or placebo OD will be given to 110 seropositive arthralgia patients in each arm during three years.

Main study parameters

The development of arthritis (≥1 swollen joint) is the primary outcome measure. Serum lipids, calculated 10-year risk of cardiovascular events (in participants aged 40 years and over), changes in cIMT and arterial stiffness are secondary outcome measures.

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Nature and extent of burden

Participants will be evaluated before initiation of therapy or placebo, every 3 months thereafter in the first year and every 6 months thereafter until a total of three years, with additional consultations by telephone at the three-month time points in between. At all visits there will be a questionnaire and physical examination (including a 44 joint examination). At each visit there will be drug dispension, and check of adverse events and compliance of drug therapy (pill count). Additional blood collection will be performed each year in Reade and in a part of the participating centers (at 0, 12, 24, and 36 months) and a carotid ultrasonography (cIMT arterial stiffness measurements) will be performed at baseline and after 36 and 48 months.

4. BACKGROUND AND RATIONALE

4.1 RA and CV disease have similar inflammatory characteristics

RA is a chronic systemic inflammatory disease, which affects approximately 1% of the population.(1) RA is characterized by swelling, tenderness, and destruction of synovial joints, leading to loss of function.(2) RA patients also suffer from various comorbidities, resulting in an increased mortality rate.(3-5) The cardiovascular (CV) risk is doubled in RA patients in comparison to the general population. This increased risk becomes apparent around the time of diagnosis of RA. (6) The cause of this enhanced risk is unknown, but inflammation is thought to play an important part. In addition, an association has been shown between future cardiovascular events and raised C-reactive protein (CRP) levels. This is in line with the accumulating evidence that inflammation has a prominent role in the development of atherosclerosis.(7-10) The increased risk is also due to increased prevalences of traditional cardiovascular risk factors in RA patients, such as dyslipidaemia, which is already present (many) years before the diagnosis RA.(10-14)

4.2 The preclinical phase of RA

Damage of bone and cartilage in joints of RA patients may begin early in the disease, often in the first year. Since structural joint damage is irreversible and can be prevented by adequate anti-inflammatory treatment, early recognition and treatment are important.(15-17) The standard strategy is prompt initiation of antirheumatic therapy as soon as the diagnosis of RA is made.(18;19) However, such therapy is often needed for prolonged periods and may cause adverse effects. Therefore, it may be advantageous to treat even earlier, when symptoms (arthralgia) may already be present, but clinical swelling of the joints has not yet occurred. In this phase, with a lower inflammatory burden, it may be possible to suppress the inflammation with a less intensive drug regimen or a shorter duration of treatment. The opportunity for such an intervention has arisen through the recognition of a preclinical or a "at risk" phase of RA characterised by the presence of auto-antibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA).(16;20-22)

Around two thirds of patients with RA have specific serologic abnormalities up to 14 years before the appearance of clinical symptoms (median 5 years). The presence of elevated serum levels of ACPA, with or without IgM-RF, in a healthy individual implies an increased risk for development of RA.(20) In a recent prospective study, it was demonstrated that 20% of ACPA positive individuals and 40% of ACPA and RF positive individuals developed arthritis within two years, of whom 90% fulfilled the 2010 ACR/EULAR classification criteria for RA. (16;21;23-25)

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In this population, we have shown that an intervention with two intramuscular injections of dexamethasone can lower antibody levels during 6 months but not prevent arthritis, which indicates that an intervention in this phase of RA needs to be longer and/or more specific.(25)

4.3 Lipid changes in (the preclinical phase of) RA

Patients with early active untreated RA exhibit reduced levels of total cholesterol, LDL cholesterol and especially HDL cholesterol.(13;26-29) Reduced HDL-cholesterol appears to be inversely correlated with inflammatory parameters, such as C-reactive protein thereby enhancing the risk of incident CV disease in RA. (27-29) This phenomenon is preceded by a decrease in HDL-cholesterol and LDL cholesterol in the preclinical phase, at least 10 years before the clinical onset of RA.(10;30) These changes have also been shown to be associated with development of RA.(14) Studies in murine models as well as epidemiological observations have shown that amelioration of this lipid profile by statins may prevent the development of RA.(1;31)

CRP is an inflammatory marker which is strongly associated with future myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death, even among apparently healthy individuals with low levels of LDL-c.(32-34)

Interestingly, a number of studies have suggested direct anti-inflammatory mechanisms for statin therapy.(32;35-38) This supports the hypothesis that lipid-lowering treatment by statins is potentially protective against subclinical inflammation and the development of RA.(10;31)

4.4 Statins as a possible preventive therapy

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are widely used lipid-lowering agents. Large clinical trials have demonstrated their efficacy in reducing cardiovascular morbidity and mortality.(1;3;12;31;32;39) Statins are known to reduce the plasma cholesterol level by inhibiting the conversion of HMG-CoA to mevalonate.(40) Statins are commonly used and generally well tolerated and cost-effective.(1;41)

Clinical and fundamental studies have shown that lipid-lowering therapy with statins not only modifies CV risk factors, but also has pleiotropic anti-inflammatory effects in rheumatic diseases, operating directly or indirectly by altering the cellular lipid milieu.(3;12) Especially one key publication of a placebo-controlled trial shows a disease-modifying effect of statins in RA (TARA-study).(1;3;40;42;43) Interestingly, the use of statins was retrospectively shown by Jick et al. to be associated with lower risk for the development of RA in patients with hyperlipidemia by a factor of 0.59.(31) In another retrospective study, Chodick, et al. also showed a decreased risk of the onset of RA in persistent statin users.(44) In this study, persistent statin users were compared to non-persistent statin users and were followed until the study outcome (RA). A hazard ratio of 0.58-0.74

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was found for RA, depending on the mean proportion of days covered (dividing the quantity of statins dispensed by the total time interval from index date to first diagnosis of RA). Protective results were also demonstrated in murine RA models with several statins.(1;43) As to the underlying mechanisms behind a possible reduction in development of arthritis, studies demonstrated a reduction of the Th1/Th2 cell ratio and CD4/CD8 ratios, RF levels, erythrocyte sedimentation rate and CRP levels after statin use, (45) implying an anti-inflammatory effect and down-regulation of the T-cell mediated immune response. There are also studies showing an anti-inflammatory and beneficial effect on onset and activity of Th1 mediated diseases such as RA. (46)

In contrast, there are also studies that have shown a neutral or even detrimental effect of statins on triggering the development of clinical arthritis. For example, a cohort study on more then 2 million patients from general practices in England and Wales found no significant association between statin use and RA. In their analysis, Hippisley-Cox and Coupland compared the risk of RA in statin users and nonusers. The study groups differed considerably in many important characteristics such as mean age, body mass index, and potentially in other important variables that were not included in the multivariable analysis (e.g. cholesterol level, LDL levels, cardiovascular diseases, and other comorbid conditions etc.) In addition, the authors reduced the statistical power of their test by stratifying the analyses by sex and five types of statins, and did not take into account the effect of time and amount of statin purchased. All of the above mentioned aspects could have masked a significant association of RA reduction.(47)

Also the two studies from de Jong et al. and Vandebriel et al. showed an increased risk on developing arthritis.(11;48) However, results from the latter studies should be appreciated with care in the light of a possible sampling bias, as data on CV risk was limited and no diagnosis verification was performed. Therefore, confounding by indication may have been the cause of these results, considering the predisposition of patients with hyperlipidemia to develop RA. (46)

Multiple studies used atorvastatin in RA patients, to measure the effect on CV risk. It appears to be a save treatment and reduced the CV risk. (3;49-51)Therefore, atorvastatin was chosen as our study drug.

5. PHARMACOLOGY AND MAIN EFFECTS OF ATORVASTATIN

5.1 Pharmacology of atorvastatin

Atorvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of atorvastatin is the liver, the target organ for cholesterol lowering. Atorvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, LDL-C, LDL-TG and increases ApoA-I. Atorvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

5.2 Dosage

The dose will be 40 mg/day.

5.3 Treatment assignment

Patients will be randomized to either atorvastatin or matching placebo in a 1:1 ratio.

5.4 Contra-indications for atorvastatin

Atorvastatin is contraindicated:

- in patients with hypersensitivity to atorvastatin or to any of the excipients (galactose intolerance, lapp lactose deficiency or glucose-galactose malabsorption).

- in patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 x the upper limit of normal (ULN).

- in patients with myopathy.

- in patients receiving concomitant ciclosporin.

- during pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.

5.5 Drug-related adverse events

The adverse reactions seen with atorvastatin are generally mild and transient. In controlled clinical trials, 5.2% of atorvastatin-treated patients were withdrawn due to adverse reactions (compared to 4.0% of the patients on placebo). Based on data from clinical studies and extensive post-marketing experience, the following list presents the adverse reaction profile for atorvastatin. Adverse reactions listed below are classified according to frequency.

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Common (≥1/100 to <1/10): nasopharyngitis, allergic reactions, hyperglycaemia, headache, pharyngolaryngeal pain, epistaxis, constipation, flatulence, dyspepsia, nausea, dairrhoea, myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain, malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia

Uncommon (≥1/1,000 to <1/100): hypoglycaemia, weight gain, anorexia, nightmare, insomnia, dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia, vision blurred, tinnitus, vomiting, abdominal pain upper and lower, eructation, pancreatitis, hepatitis, urticarial, skin rash, pruritus, alopecia, neck pain, muscle fatigue

Rare (≥1/10,000 to <1/1000): thrombocytopenia, peripheral neuropathy, visual disturbance, cholestatis, angioneurotic oedema, dermatitis bullous including erythema multiforme, stevens-johnson syndrome, toxic epidermal necrolysis, myopathy, myositis, rhabdomyolysis, tendonopathy

Very rare (<1/10,000): anaphylaxis, hearling loss, hepatic failure, gynecomastia

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent.

5.6 Management before and while on treatment

5.6.1 Before treatment

Atorvastatin, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with:

• history of liver disease

• personal or family history of hereditary muscular disorders

• previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate

• alcohol abuse

• age >70 years

• situations where an increase in plasma levels may occur (SLOC1B1 polymophism)

• concomitant use of Tipranavir, Telaprevir, Ciclosporin, Lopinavir, Clarithromycin, Saquinavir, Darunavir, Ritonavir, Itraconazole, Fosamprenavir, Nelfinavir, Grapefruit Juice, Diltiazem, Erythromycin, Amlodipine, Cimetidine, Antacid suspension of magnesium and aluminium hydroxides, Efavirenz, Rifampin, Gemfibrozil, Fenofibrate or Digoxin.

In view of the above, before inclusion in the study the following blood tests will be performed: RF, ACPA, total-, HDL- an LDL-cholesterol, apolipoprotein A, apolipoprotein B, HbA1c, ALAT, creatinine,

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CK, ESR and CRP. Inclusion will not take place if: ALAT is >3 x ULN and/or CK levels are >3 x ULN, adjusted for gender and race (see table, >3 x 97th Percentile). In case of a possible transient cause of CK such as trauma, injection or strenuous exercise, CK can be repeated after one week's rest, after which a level <3x ULN can lead to inclusion.

Distribution of Serum CK in Different Population Groups

	Median	97th Percentile
All subjects	111	460
Women	95	349
Men	143	616
White	88	286
Women	72	201
Men	110	322
South Asian	104	382
Women	87	313
Men	143	641
Black	149	627
Women	124	414
Men	213	801

Brewer

LM Brewster, G Mairuhu, A. Sturk, et al; Distribution of creatine kinase in the general population: implications for statin therapy. AM Heart J. 2007 Oct; 154(4): 655-61

5.6.2 While on treatment

After three months of treatment, there will be another blood test for assessment of CRP, ESR, ALAT and creatinine. CK levels will be repeated if elevated at baseline or if subjects complain about myalgia. Some evidence suggests that statins as a class raise blood glucose in some patients at high risk of future diabetes mellitus (DM). Patients at risk (BMI >30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines. However, several studies indicate that the risk of diabetes mellitus by statin treatment is relatively low: in the JUPITER study, the reported overall frequency of diabetes mellitus was 2.8% in rosuvastatin and 2.3% in placebo-treated patients, mostly in patients with fasting glucose 5.6 to 6.9 mmol/l.(33) In addition, Sattar et al. performed a meta-analysis on the risk of development of diabetes mellitus in patients given statins. 91140 participants were included, of whom 4278 developed diabetes during a mean of 4 years (odds ratio [OR] 1·09; 95% CI 1·02-1·17). This equated

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to a number needed to treat of 255 patients treated for 4 years to see one additional case of diabetes. Therefore, statin therapy is associated with a slightly increased risk of development of diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events.(52)

5.7 Subject compliance

Compliance will be evaluated at all visits. Subjects will be asked to return unused medication. Nurses will count and log returned medication and record returns. Any compliance issues reported by the subject or by other medical professionals will be reported in the CRF.

6. HYPOTHESIS AND OBJECTIVES

6.1 Hypothesis

The hypothesis of the present study is that the use of atorvastatin in persons at high risk of RA is associated with a reduction in the development of arthritis. High risk is defined as high ACPA level (>3x cut-off) and/or presence of ACPA and RF, which equals to a risk of 55% of developing arthritis within three years (not yet published data from our prospective seropositive arthralgia cohort). Arthritis is defined as presence of 1 or more swollen joints at clinical examination.

In addition, we monitor lipid lowering effects and CV risk reduction, measured with blood samples (lipid profile), cIMT and arterial stiffness of the carotids as well as the occurrence of cardiovascular events. Cost-effectiveness is measured as well.

6.2 End points

Primary

The occurrence of clinical arthritis confirmed by a rheumatologist participating in the study.

Secondary

Effect on improvement of lipid profile, (sub)clinical CV risk, inflammatory parameters and changes in cIMT and arterial stiffness.

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7. STUDY POPULATION

7.1 Inclusion and exclusion criteria

Patients who are seropositive according to the inclusion criteria with or without artralgia will be recruited from the outpatient clinic of the departments of rheumatology of Jan van Breemen Research Institute | Reade; Amsterdam, the VU University Medical Center (VUmc); Amsterdam, Bernhoven hospital; Uden, Maasstad Hospital; Rotterdam, Sint Maartenskliniek; Nijmegen and Rijnstate Hospital; Arnhem; Zuyderland medisch centrum; Heerlen. Other centers will be added if the inclusion rate is too slow.

Inclusion criteria

1) Age >= 18 years

2) Seropositive

-IgM-RF and ACPA positive OR

-High ACPA titer (>3x cut-off)

3) With or without current joint pain, but without current clinical synovitis (ultrasound exam should not be performed in case of doubt, since US was shown to be often false-positive in this patient group)

4) Written informed consent

Exclusion criteria

1) Patients with synovitis during clinical examination (any of 44 joints of DAS) at inclusion or synovitis in the past during clinical examination by a rheumatologist.

2) Patients with typical RA erosions on X-rays of hand and feet.

3) In case of inclusion depending on the presence of RF, the presence of situations with possible false-positive RF: known active infection with hepatitis C or Ebstein-Barr virus or recent radiotherapy.

4) Use of statins or other lipid-lowering agents within the last three months.

5) A history of previous use of statins discontinued due to side effects.

6) Patients with an indication for statin therapy according to local guidelines. All patients will be screened pior to randomisation, patients who fall into this category (SBD>180 mmHg, TC/HDL> 8.0 or have a cardiovailair risk ≥20% (only for patients between 40-70 years old) with SBD>140 mmHg and/ or LDL>2,5 mmol/L (see appendix H)) will be referred to the general practitioner with treatment advice).

7) Previous use of DMARDs other than hydroxychloroquine, or use of hydroxychloroquine within the last three months.

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8) A history of oral or parenteral use of corticosteroids within the last 12 weeks used to treat the current episode of musculoskeletal symptoms.

9) Subjects with current severe, progressive, or uncontrolled hepatic disease (ALT>3x ULN), CK >3x ULN, hematologic disease, gastrointestinal disease, (diabetes with a serum glucose >7.0 mmol/L), pulmonary, cardiac, neurologic, or cerebral disease which, in the opinion of the investigator, might place a subject at unacceptable risk when participating in the study.

10) Subjects who are pregnant or who are breastfeeding or wish to become pregnant.

11) Subjects who currently abuse recreational drugs, or drink alcohol in excess (defined for the purposes of this trial as ≥ 21 units of alcohol per week; one unit = 1 glass of wine (125 mL) = 1 measure of spirits = ½ pint of beer).

12) Subjects who have a limited life expectancy.

13) Subjects who are unable to fill out the questionnaires.

14) Subjects who are using ciclosporin (which interacts with statins).

7.2 Participant recruitment

The study will recruit 220 study subjects who are at high risk of developing RA. Unlike patients with established disease, participants may be recruited through a range of ethically approved methods, including any one of the following:

- Rheumatology outpatient clinics of the VU medical center, Jan van Breemen Research Institute | Reade, Bernhoven hospital, Maasstad Hospital, Sint Maartenskliniek, Zuyderland MC, and Rijnstate Hospital,
- Referrals to recruiting centres from other Rheumatology out-patient clinics
- Referrals from GP practices
- In response to advertising in the primary or secondary care sector, via posters or leaflets (eg displayed in the waiting room of rheumatology outpatients departments or GP surgeries)
- Through existing research databases, including but not confined to first degree relatives of patients with RA, or cohorts of subjects known to carry serum ACPA / RF
- Patient support groups via patient magazines, society websites and by direct mailing to members
- First degree relatives (FDR) of patients with RA, who wish to be tested for ACPA
- Media campaigns aimed directly at FDRs. This may include press releases, media advertisements (newspaper, radio, web-based) or editorial features (newspaper, radio, television)
- Via other publicity opportunities that may be identified by the study team

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If an individual is interested in participating, a patient information sheet will be given. The patient will then be contacted by telephone at least 24 hours after receiving the patient information sheet to see if they are interested in participating in the trial. If they are, a screening visit will be arranged. Details of all patients approached to participate in the trial will be documented on the trial screening logs.

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8. METHODS OF INVESTIGATION

8.1 Trial design

A multicenter double-blind randomized placebo controlled clinical trial of atorvastatin in high-titer ACPA or ACPA and RF positive subjects to prevent the development of RA.

8.2 Study design

8.2.1 Screening visit

Possible participants as identified by serology and the absence of clinical arthritis are referred to the study physician. After receiving the study information and expressing an interest to participate, candidates are invited for a screening visit, which will include a questionnaire (age, sex, symptom type and duration, alcohol intake, smoking, family history, medical history, medication use, comorbidity, cardiovascular disease), physical examination (DAS44, blood pressure, ABI, weight, height and waist-hip ratio), ECG, blood collection of the following items: RF/ACPA, CRP, ESR, total-, HDL- and LDL-cholesterol, triglycerides, apolipoprotein A and apolipoprotein B, HbA1c, CK, ALAT and serum creatinine. Extra plasma, serum, DNA and RNA will be stored at -80 degrees Celsius for future markers of interest in those centers who wish to participate in this. At least part of the material will be shipped to Reade for central storage and analysis. After reviewing the results of the lab tests, eligibility for the trial can be determined.

8.2.2 Baseline visit: inclusion and randomisation

Patients who are eligible are invited for the baseline visit. Before randomisation they undergo another physical examination of the joints. This assessment will not be necessary if the baseline visit is scheduled within two weeks of the screening visit. If there are no swollen joints, the patient will fill out questionnaires (EQ5D, arthralgia symptoms questionnaire (appendix G, currently being developed) and HAQ) and a carotid ultrasound will be performed, which is optional per center (intima-media thickness, estimated pulse-wave velocity and augmentation index). Then randomisation will take place at the pharmacy at Reade, after which the medication (atorvastatin or placebo) will be started.

8.2.3 Follow-up visits

After initiation of therapy every 3 months in the first year and every 6 months thereafter (with additional consultations by telephone at the three-month time points in between) there will be a follow-up visit, including EQ5D, HAQ, symptom questionnaire, cardiovascular disease questionnaire, physical examination (DAS44, blood pressure, weight, height and waist-hip ratio). Every visit there will be adverse effect evaluation, pill counting and drug dispension. On a yearly basis (0, 12, 24 and

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36 months) blood collection (optional per center) will be done (RF/ACPA, CRP, ESR, total-, HDL- and LDL-cholesterol, triglycerides, apolipoprotein A and apolipoprotein B, HbA1c, ALAT and serum creatinine). Three months after starting the medication (or placebo) there will be an additional blood test (ALAT, creatinine, ESR and CRP) and at any other time point an additional blood test for CK will be performed in case of suspected statin myopathy. After four years (one year after stopping the medication), patients will have another visit to determine possible loss of effect of secondary end points. At baseline and after 3 and 4 years a carotid ultrasound will be performed.

In case of arthritis development between visits, an extra visit can be planned. After the development of arthritis, the primary endpoint will be met and the subject will discontinue the study.

This schedule is for subjects who are included in Reade. For subjects who are included in one of the other hospitals, there is the possibility for a simplified schedule. See appendix A for both study design schedules.

8.2.4 Handling of side effects

Special attention is needed for musculoskeletal side effects of atorvastatin, since the symptoms thereof can be similar to the symptoms of arthralgia that led to the inclusion in the study. In general one can say that the symptoms of the study disease will be mainly in the joints (arthralgia) and of the study drug mainly in the muscles (myalgia), but some overlap may occur. Therefore, myalgia newly appearing during the study would raise a suspicion of statin-induced myopathy.

Atorvastatin will be discontinued in case of side effects that are deemed serious by the study physician or nurse, after consulting the local principal investigator. Reasons can be a severe allergic reaction, intense myalgia with or without an increase of CK levels. If subjects experience more than minor side-effects attributed to the study drug by patient or study nurse/physician, the patient will stop taking the medication for four weeks. If there is no change after four weeks, the symptoms are concluded not to be caused by the study drug and the study drug will be reinstituted. If the symptoms have decreased or disappeared after four weeks, there will be a rechallenge. If the symptoms return, the medication will be stopped again until all the symptoms attributed to the study drug have disappeared. Then the patient will restart the medication, but half a tablet every day, which equals a 50% dose decrease. If the subjects again experience symptoms attributed to the study drug after this change in schedule, they will stop taking the medication. However, all patients who have stopped the medication will be requested to complete the study visits.

8.3 Randomisation and drug dispension procedure

Patients will be randomized to atorvastatin and placebo in a 1:1 ratio. The randomisation will be in blocks of 10 subjects and will take place in the pharmacy at Reade. After the randomisation, the

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pharmacy will give patients the atorvastatin or placebo at Reade. For the other centers the pharmacy at Reade will send the medication (every three months) by mail to the patients home adress. A few days after sending, there will be a phonecall from the researcher at Reade, after this the patient can start taking the medication.

The pharmacy at Reade will be keeping the randomisation list. A copy will be stored at a central place at Reade, only accessible for the previously chosen independent persons. The data will be unblinded when the last patient has finished the study and the analysis of the primary end point has taken place. The investigator will be responsible for analyzing the data.

The research physician, research nurse and the patients will be blinded for the study medication. The atorvastatin and placebo tablets will have a similar appearance and will be distributed in the same box, and are thus unidentifiable for both patient and physician.

8.4 Withdrawal of subjects

Patients will be free to withdraw at any time. Patients wishing to withdraw from the study will be asked to complete a withdrawal questionnaire including reasons for withdrawal. Patients that do withdraw will be invited to return for milestone assessments so that data may be collected and changes in their disease can be assessed; it will be made clear to them that this is entirely at their free will.

Subjects MUST discontinue investigational product (or placebo) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any serious clinical adverse event, serious laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Development of a concurrent illness that would exclude trial entry, except RA.
- Failure to comply with the allocated treatment regime.
- In the Principal Investigator's opinion, the need to administer concomitant medication not permitted by the trial protocol.
- Pregnancy (women will be instructed to contact the investigator or study staff immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation.)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.

If a subject withdraws before completing the study, the reason for withdrawal must be documented appropriately.

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If subjects temporarily did not use the medication, they are able to continue the study if the time that they did not use the medication is less than 120 days.

8.5 History and physical examination

Demographic and clinical data will be collected by questionnaires and include age, sex, symptom type and disease duration, alcohol intake, smoking, family history, medical history and comorbidity and concomitant medication use.

The following questionnaires will be done to evaluate quality of life, functional capability and disease activity, respectively: EQ5D, HAQ, cardiovasculair disease questionnaire as well as a questionnaire for arthralgia characteristics.

A physical examination includes blood pressure, weight, height and waist-hip ratio and DAS44.

8.6 ECG

A standard 12-lead electrocardiogram (ECG) will be made of each patient at baseline. This ECG will be used to see if there is previous cardiac disease. If an abnormality is noted the ECG will be analysed by a cardiologist.

8.7 Ultrasound examination

High-resolution carotid ultrasonograhy will be performed (in Reade with the Aloka Ultrasound system) based on classical high-resolution echotracking technology. Properties of the right and left common carotid far wall (10 mm proximal to the flow divider) will be determined with the use of an ultrasound scanner equipped with a 7.5MHz linear probe (Aloka Co Ltd., Tokyo, Japan). This system enables the determination of carotid intima-media thickness (cIMT) in the common carotid arteries, estimated pulse-wave velocity (generalized arterial stiffness) and estimated augmentation index (local arterial stiffness) with a very high precision and reproducibility (also see appendix B). As the ultrasound examination will be performed at the Jan van Breemen Research Institute | Reade as well as in the University Medical Center Groningen, we will perform an inter-observer variability test to assess the reproducibility of the performance.

8.8 Laboratory measurements

Blood samples will be collected yearly for measurement of autoantibodies (ACPA measured as anti-CCP ELISA and RF measured as IgM-RF ELISA – comparison of assays between centers will be performed beforehand), serum creatinine, ALAT, HbA1c and inflammatory parameters (CRP and ESR). Extra blood will be stored to determine a lipid profile (total-, HDL- and LDL-cholesterol,

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triglycerides, apolipoprotein A and apolipoprotein B) when the study is finished, to guarantee this study will be dubbelblind. Only on baseline a lipid profile will be analysed with the other measurements.

Extra serum, plasma and RNA will be stored yearly at -80° in Reade and if wished also at the local biobank.

When complaints of increasing myalgia occur, an additional CK measurement will be performed to evaluate myopathy or rhabdomyolysis.

9 SAFETY REPORTING

9.1 Definition of adverse events and serious adverse events

An adverse event (AE) is defined as any appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug, even if the event is not considered to be correlated to the study drug. The period of observation for adverse events extends from the time the patient gives informed consent until he or she undergoes the final examination as part of the study. Adverse events occurring after this period should also be mentioned in the CRF, if the adverse event comes to the knowledge of the investigator.

All adverse events, whether considered associated with the use of the study medication or not, must be followed to a satisfactory conclusion, i.e. until they return to baseline, become stabilized or until there is a satisfactory explanation for the changes observed. In case of death a full pathologist's report should be supplied, if possible. All findings must be reported in the case record form and in the patient's medical records.

An adverse event is considered a serious adverse event (SAE) if it meets the following criteria:

- any event that is fatal or life threatening

- any event that is permanently or significantly disabling

- any event that requires or prolongs hospitalization

- any event that involves cancer or congenital anomaly

- any event that occurs with overdose (any dosage higher than that recommended in the Investigator's Brochure or package insert)

- any event that suggests a significant hazard

All SAE will be will be reported to the METC within 7 days (if life threatening) or 15 days (if not life threatening) through ToetsingOnline. Regardless of the classification of an adverse event as serious (see above), the severity of all adverse events must be assessed as mild, moderate or severe.

Severe: the adverse event causes considerable interference with the subject's usual

activities and may be incapacitating or life-threatening

Moderate: the adverse event causes the subject discomfort and interrupts the subject's usual activities

Mild: the adverse event is transient and easily tolerated by the subject

Furthermore, the investigator will assess the relationship of the adverse event to the use of the study drug into:

Not related: the adverse event is due to an underlying or intercurrent illness or effect of another drug and is not related to the study drug

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<u>Probably not related:</u> the adverse event has little temporal relationship to study drug and a more likely etiology of the adverse event exists

<u>Possibly related:</u> the adverse event has a strong temporal relationship to the study drug and an alternative etiology is less likely

<u>Probably related:</u> the adverse event has a strong temporal relationship to the study drug or recurs on re-challenge and another etiology is unlikely

If in the opinion of the investigator the adverse event is considered (probably) not related, an alternative etiology must be provided.

9.2 Reporting of adverse events

<u>Serious adverse events</u>

All serious adverse events which occur from consent until 30 days after stopping of the trial, whether considered to be associated with the study medication or not MUST be reported by participating sites within 24 hours or at the latest on the following working day to the primary site, Reade. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event. Information about all SAE's is collected and recorded on the Serious Adverse Event Report Form. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

<u>Suspected unexpected serious adverse reactions (SUSAR)</u>

Adverse reactions are all untoward and unintended responses to a medical product related to any dose administered. Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (Summary of Product Characteristics (SPC) for an authorised medicinal product). All SUSARs will be reported within 7 days (if life threatening) or within 15 days (if not life threatening) using ToetsingOnline to LAREB, CBG, METC and CCMO. For fatal or life threatening cases the expedited reporting will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

<u>Non-serious adverse events</u>

These are to be documented in the CRF.

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Adverse events occurring after the period of observation

Any adverse event occurring at any time after the end of the study and considered to be caused by the study medication - and therefore a possible adverse drug reaction - must be reported as above.

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10. STATISTICAL METHODS

10.1 Power calculation

In the retrospective population study by Jick, a 38% risk reduction of developing RA was noted in persons with hyperlipidaemia using statins versus those not on statins. Patients with high ACPA and/or with ACPA and RF have a risk of 55% of developing RA within three years.(31) Therefore we conservatively estimate (as the level of subclinical inflammation is expected to be higher in seropositive arthralgia patients compared to groups with hyperlipidemia in the general population) a risk reduction from 55% to 34%. For a study with a power of 0.80 and two-sided p-value of 0.05 and after the continuity correction, the necessary sample size becomes 97 individuals in each arm. Accounting for 10% loss to follow-up or drop out, as is our current experience, the final sample size will be 110 individuals in each arm. Expected differences in changes in cIMT can be found with 68 individuals per arm.

10.2 Statistical analyses

After data collection, descriptive statistics (means ± standard deviation or median and interquartile range, as appropriate) will be used to describe the whole study population with regard to demographics, anthropometric measurements, laboratory values, cIMT and arterial stiffness and inflammatory activity as assessed by a DAS44, EQ5D, HAQ and arthralgia symptom questionnaire.

Mean change in the lipid profile, inflammatory activity, cIMT and arterial stiffness will be determined. Comparisons will be made between patients receiving atorvastatin, and patients receiving placebo.

For primary outcomes, Chi squares test and logistic regression analyses will be used. For secondary outcomes a paired-samples t-test will be used, while logistic and linear regression analyses will be used to investigate the relationship between lipids and inflammatory parameters. To investigate these associations over time and their relationship with reduced development of arthritis, GEE analysis will be used.

An interim-analysis will be performed after 95% of participants have been included, if needed additional patients will be included.

11. ETHICAL AND LEGAL ASPECTS

11.1 Good clinical practice

The procedures set out in this study protocol are designed to ensure that the sponsor and the investigator abide by the principles of the good clinical practice guidelines of the European Community and the Declaration of Helsinki in the conduct (53), evaluation and documentation of this study. The study will also be carried out in keeping with local legal requirements. The study will be entered into the Netherlands Trial Register.

11.2 Informed consent

Before undergoing any study procedure, the patient must have given his/her written informed consent to participate after the nature, scope and possible consequences of the clinical study have been explained in an understandable way. The patient will also be given an information sheet about the study and a copy of the signed informed consent form. The terms of the consent and when it was obtained must also be documented in the case report form.

11.3 Approval of the study protocol

Before the start of the study, the study protocol and/or other appropriate documents will be submitted to the METC and/or the authorities, in accordance with local legal requirements.

11.4 Confidentiality

All patient names will be kept secret. The number allotted to them during the study will identify patients throughout documentation and evaluation. The patients will be told that all study findings will be stored and handled in strictest confidence.

The signed informed consent forms remain with the investigator. The investigator must obtain a correctly completed informed consent form for each patient included in the study. He/she also agrees to allow these to be inspected on request. The investigator will maintain a personal list of patient numbers and patient names to enable records to be found at a later date. Both the consent forms and the personal list of patient numbers will be kept for 20 years.

11.5 Liability and insurance

The civil liability of the investigator, the persons instructed by him/her and the hospital, practice or institute in which they are employed and the liability of the institutes in respect of financial loss due to personal injury and other damage which may arise as a result of the carrying out of this study are governed by the applicable law.

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The institutes have taken out reasonable third-party liability insurance cover. As a precautionary measure, the investigator, the persons instructed by him/her and the hospital, practice or institute are included in such cover in respect of work done by them in carrying out this trial to the extent that the claims are not covered by their own professional indemnity insurance.

Such insurance covers claims provided that:

- the instructions and procedures laid down in the study protocol are followed precisely and the investigator acts with the necessary care
- the patients do not undergo any other medical treatment without the previous consent of the investigator and that the investigator has informed patients to that effect
- the patient informs the investigator immediately of any unforeseeable adverse events
- the physical injury or other damage does not arise as a result of any gross negligence, willful act or omission

11.6 Use of study findings

By signing the study protocol, the investigator agrees with the use of results of the study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the investigator's name, address, qualifications and extent of involvement.

The findings of this study will be published in a scientific journal and presented at scientific meetings.

11.7 Protocol amendments

Amendments should be made only in exceptional cases once the study has started. Changes must be agreed to in writing, and signed, by all parties concerned. The changes then become part of the study protocol.

The METC must be informed of all amendments and if necessary approval must be sought for ethical aspects. Approval must also be obtained from the authorities if necessary.

11.8 Possible discomfort for the subjects

There are aspects to this protocol that may cause some discomfort to the subjects:

- The measures are clustered together to ensure that the subjects have no more visits than 4 times the first year and 2 times the second and third year and 1 time in the fourth year (see time schedule appendix A). All measurements will be performed by trained research assistants and PhD-students to make each visit as comfortable as possible.

- An amount of no more than 75 ml each time of blood will be withdrawn by means of vena puncture. This could cause a bruise.

- During each vascular measurement, the subject has to stay in a fixed, immobilised position for a maximum of 15 minutes.

-During an ECG, the subject has to stay in a fixed, immobilised position for a few minutes.

- When measuring blood pressure, the inflation of the cuff may cause transient paresthesia in the hand.

11.9 Unexpected findings

In case of an unexpected finding that may be new and could interfere with the health of the subjects, the participant and (if allowed by the subject) his/her family doctor will be informed in writing. This policy is also outlined in the subject information letter.

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12. STUDY DOCUMENTATION, CASE REPORT FORMS AND RECORD KEEPING

12.1 Investigator's files/retention of documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories (1) Investigator's Study File, and (2) patient clinical source documents.

The investigator's Study Files will contain the protocol/amendments, Case Report and Query Forms, METC and governmental approval with correspondence, approved informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, and special assessment reports, signed informed consent forms, consultant letters, and patient screening and enrolment logs. The Investigator must keep these two categories of documents on file for at least 20 years after completion or discontinuation of the study. After that period of time the documents may be destroyed per local regulations.

12.2 Case report form (CRF)

For each patient enrolled, a CRF must be completed and signed by the principal investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the CRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

All forms should be typed or filled out using indelible ink, and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialled and dated by the investigator or his/her authorized delegate.

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13 INVESTIGATIONAL SCHEME

13.1 Project plan

This study concerns a multicenter double-blind randomized placebo-controlled trial. The study will start in Reade, Jan van Breemen Research Institute and secondly in the VUmc, Maasstad hospital, Sint Maartenskliniek, Rijnstate hospital, Bernhoven ziekenhuis, and Zuyderland MC.

A total of 220 subjects will be enrolled in two years and followed during 4 years per person. The extensive medical examination will require 4 visits in the first year and 2 visits and 2 phone calls in the two years after that and 1 visit in the fourth year. In the first months, the study add-on protocol will be finalized and submitted to the local Medical Ethics Review Committee (METc) for approval. After approval by the local medical ethics research committees, the study will be carried out at the VUmc, Maasstad hospital, Bernhoven hospital, Sint Maartenskliniek, Rijnstate hospital, and Zuyderland MC. For these hospitals there is a simplified schedule, if desired (see appendix A).

The measurements of blood tests, cIMT and arterial stiffness will be performed once every year locally. In the 4th year the data-analyses will be performed and the results will be performed and the results will be presented in publications and in a thesis.

13.2 Grants

This study is partially funded by the Dutch Arthritis Association (Reumafonds).

13.3 Infrastructural arrangements

The collaborating departments have the logistics necessary for this study and all of the above described techniques are operational. The clinical part of the study will be conducted at the department of rheumatology. Biochemical and haematological variables will be determined at the department of clinical chemistry. cIMT, arterial stiffness and ECG will be performed at the department of rheumatology.

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APPENDIX A – Trial flowchart and schedule of visits

Schedule in Jan van Breemen Research Institute | Reade

Months	-1	0	3	6	9	12	15	18	21	24	27	30	33	36	48
Visit	1	2	3	4	5	6	7*	8	9*	10	11*	12	13*	14	15
Introduction and informed consent	X														
Inclusion and exclusion criteria check	X														
Medical History	X			X		X				X				X	X
Physical examination	X	X**	X	X	X	X		X		X		X		X	X
Drug dispension		X	X	X	X	X		X		X		X			
Adverse events and pill count			X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X														
Carotids ultrasound		X												X	X
X-rays of hands & feet	X														
Lab tests	X***		X****			X*****				X*****				X*****	X*****
Future biomarkers (blood)*****	X					X				X				X	X
DAS-44	X		X			X				X				X	X
Tender and swollen joint count		X		X	X			X				X			
Cardiovascular disease questionnaire	X					X				X				X	X
EQ5D		X	X	X	X	X		X		X		X		X	X
Symptoms questionnaire		X	X	X	X	X		X		X		X		X	X
HAQ		X	X	X	X	X		X		X		X		X	X

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* telephone consultation

** Physical examination will not be necessary if the baseline visit is scheduled within two weeks of the screening visit.

*** extended blood test: RF, ACPA, CRP, ESR, total-, HDL- and LDL-cholesterol, triglycerides, apolipoprotein A and apolipoprotein B, HbA1c, ALAT, serum creatinine and CK

**** abbreviated blood test: ALAT, creatinine, ESR, CRP

***** extended blood test: RF, ACPA, CRP, ESR, ALAT, serum creatinine and CK*****Lab reference samples at annual visits: Serum 3 x 2 and 1x 1,5 ml tube, Plasma 1 x 2 ml tube, EDTA 1 x 6 ml tube, PAXgene 1 x3 ml tube, citrate 1 x 2,7 ml tube

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Abbreviated schedule for other participating centers

For every centre it is optional if they want/ are able to perform a carotid ultrasound. As well as to collect future biomarkers (urine and blood) on a yearly

basis (as the schedule in Reade)

Months	-1	0	3	6	9	12	15	18	21	24	27	30	33	36
Visit	1	2	3	4	5	6	7*	8	9*	10	11*	12	13*	14
Introduction and informed consent	X													
Inclusion and exclusion criteria check	X													
Medical History	X			X		X				X				X
Physical examination	X	X**	X	X	X	X		X		X		X		X
Drug dispension		X	X	X	X	X		X		X		X		
Adverse events and pill count			X	X	X	X	X	X	X	X	X	X	X	X
ECG	X													
X-rays of hands & feet	X													
Lab tests	X***		X****											
Future biomarkers (blood)****	X													
DAS-44	X		X											
Tender and swollen joint count		X		X	X	X		X		X		X		X
Cardiovascular disease questionnaire	X					X				X				X
EQ5D		X	X	X	X	X		X		X		X		X
Symptoms questionnaire		X	X	X	X	X		X		X		X		X
HAQ		X	X	X	X	X		X		X		X		X

40

* telephone consultation

** Physical examination will not be necessary if the baseline visit is scheduled within two weeks of the screening visit.

*** extended blood test: RF, ACPA, CRP, ESR, total-, HDL- and LDL-cholesterol, triglycerides, apolipoprotein A and apolipoprotein B, HbA1c, ALAT, serum creatinine and CK

**** abbreviated blood test: ALAT, creatinine, ESR, CRP****Lab reference samples at annual visits: Serum 2 x 2 ml tube, Plasma 1 x 2 ml tube, EDTA 1 x 6 ml tube

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APPENDIX B - STANDARD OPERATIONAL PROCEDURE (IN DUTCH)

Intima-media thickness, estimated pulse wave velocity and augmentation index

Doel: Uit prospectief onderzoek is gebleken dat een verdikte vaatwand van de grote arteriën of de aanwezigheid van lokale plaques in deze arteriën, direct in verband staan met cardiovasculaire risico factoren zoals roken, verhoogd LDL cholesterol en leeftijd. Ook is er een relatie tussen een verdikte media intima en het risico op een myocardinfarct en een beroerte bij volwassenen. De B-mode sonografie van de arteria carotis communis stelt ons in staat om, op een niet invasieve wijze, een duidelijk visueel beeld te vormen van de ruimte tussen de adventitia en intima, ook wel carotid intima-media thickness (cIMT) genoemd. Door een gedigitaliseerde beeldverwerking is het mogelijk deze ruimte tussen intima en adventitia zeer nauwkeurig te meten.

Verantwoordelijkheden:

De onderzoeker is verantwoordelijk voor:

- Een correcte voorbereiding van de procedure, document, kamer en toestel.

- Een volledige uitleg van de procedure aan de onderzoekspatiënt.

- Het correct uitvoeren van de beschreven procedure.

- Het correct en leesbaar registreren van de gemeten resultaten.

Benodigdheden:

- Bloeddrukmeter

- Hitachi Aloka ProSound F75, Biomedic B.V.

- 3 ECG klemmetjes in groen, rood en zwart, voor de onderarmen en de rechterenkel.

- High viscositeit gel.

- Beschermdoekjes of handdoeken.

- Desinfectantia voor transducer.

Meten van intima-media thickness (IMT):

1. De proefpersoon wordt geïnformeerd over de te volgen procedure.

2. De proefpersoon neemt een comfortabele, liggende positie op het bed in.

3. De ECG stekker wordt in het echoapparaat gedaan (onder de klep). De ECG klemmen worden na het aanbrengen van echogeleide gel bevestigt aan de rechteronderarm (rode klem), linkeronderarm (groene klem) en rechteronderbeen/enkel (zwarte klem).

4. Na minimaal 10 minuten rust, wordt rechts de bloeddruk aan de arteria brachialis gemeten.

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5. Het meettoestel wordt opgestart en de instellingen gecontroleerd. Het ID van de deelnemer wordt ingevoerd, bestaande uit deelnemernummer, naam van het onderzoek en de datum van het onderzoek.

6. Op het beeldscherm wordt op [Next page] gedrukt. Daarna wordt de preset [Carotis (20)] gekozen.

7. High viscosity ultrasound-gel wordt aangebracht op de echokop (Probe 5411) en de echokop word geplaatst op de hals, ventraal van de musculus sternocleidomasteoidius.

8. Op het beeldscherm worden de arteria carotis communis, bifurcatie en interne arteria carotis in beeld gebracht. Atherosclerotische plaques in dit gebied worden geïdentificeerd en genoteerd. Een meetlijn word getekend vanaf het punt waar de bifurcatie eindigt tot 10mm proximaal. Dit is het punt waar de IMT word gemeten.

9. Terwijl men met de echokop corrigeert, wordt op het beeldscherm de intima en media-adventitia interface gevisualiseerd, waarna voor 10 seconden de opname opgeslagen word door op het toetsenbord op de knop [STORE] te drukken en 10 seconden te wachten. Daarna wordt op de knop [► | ◄] gedrukt om het beeld te pauzeren.

10. De opgenomen video wordt teruggedraaid en op de R-top van het ECG word het beeld stilgezet. Men drukt op het beeldscherm op [cc-IMT], en op het scherm verschijnt een rechthoek met drie lijnen. Met behulp van de trackball wordt de linkerpunt van de middelste lijn gezet op de lumen-intima interface en men drukt op [Enter]. Daarna zet men de rechterpunt van de middelste lijn op de media-adventitia interface enkele millimeter verderop en men drukt op [Enter]. Dit is de regio waarbinnen de IMT gemeten word. IMT en diameter worden automatisch berekend als men de tweede keer op [Enter] heeft gedrukt.

Meten van estimated pulse-wave velocity en augmentation index:

1. De proefpersoon wordt geïnformeerd over de te volgen procedure.

2. De proefpersoon neemt een comfortabele, liggende positie op het bed in..

3. De ECG stekker wordt in het echoapparaat gedaan (onder de klep). De ECG klemmen worden na het aanbrengen van echogeleide gel bevestigd aan de rechteronderarm (rode klem), linkeronderarm (groene klem) en rechteronderbeen/enkel (zwarte klem).

4. Na minimaal 10 minuten rust, wordt rechts de bloeddruk aan de arteria brachialis gemeten.

5. Het meettoestel wordt opgestart en de instellingen gecontroleerd. Het ID van de deelnemer wordt ingevoerd, bestaande uit deelnemernummer, naam van het onderzoek en de datum van het onderzoek.

6. Op het beeldscherm wordt op [Next page] gedrukt. Op het beeldscherm wordt de preset [eTracking (26)] gekozen..

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7. Door op knop [Physio2] op het beeldscherm te drukken kan men de kwaliteit van het ECG signaal controleren. Hierna wordt op de knop [ET] gedrukt waarna de meting verricht kan worden.

8. High viscosity ultrasound-gel wordt aangebracht op de echokop (Probe 5411).

9. Op het beeldscherm worden de arteria carotis communis, bifurcatie en interne arteria carotis. Atherosclerotische plaques in dit gebied worden geïdentificeerd en genoteerd. Een meetlijn wordt getekend vanaf het punt waar de bifurcatie eindigt tot 10mm proximaal. Dit is het punt waar de vaatstijfheidsindices worden gemeten.

10. In het linkerbeeld staan twee lijnen. Met behulp van de trackball wordt de bovenste lijn verschoven tot op de bovenste lumen-intima interface en aangeklikt door middel van [Enter]. Daarna wordt de onderste lijn op de onderste lumen-intima interface gezet en aangeklikt door middel van [Enter]. Het beeld wordt hierna automatisch opgenomen.

11. Na het indrukken van de knop [STORE], volgt het programma waar de bloeddruk ingevoerd kan worden[Epressure] en de arteriële polsgolven die kwalitatief goed zijn geselecteerd worden. Hierna volgt een automatische berekening van de estimated pulse-wave velocity en augmentatie index.

APPENDIX C VISUAL ANALOGUE SCALES

VASSEN

-Hoeveel **pijn** had u de afgelopen week gemiddeld ten gevolge van uw **gewrichtsklachten**?

|⊢————————————————————————|

(VAS pijn: …... mm)

Geen pijn   Ergst voorstelbare

-Heeft u de afgelopen week last (gehad) van ochtendstijfheid?   ja □   nee □

-Duur ochtendstijfheid totdat u zo soepel was als normaal voor de dag ....minuten

-Hoe **erg** ervaart u deze **ochtendstijfheid**?

|⊢————————————————————————|

(VAS OS: …... mm)

Niet erg   Ergst voorstelbaar

-Hoe moe was u de afgelopen week?

|⊢————————————————————————|

(VAS moeheid: … mm)

Niet moe   Ergst moe

- Hoe voelde u zich over het **algemeen** de **afgelopen week** ten gevolge van uw **gewrichtsklachten**?

|⊢————————————————————————|

(VAS global: …... mm)

Zeer goed   Zeer slecht
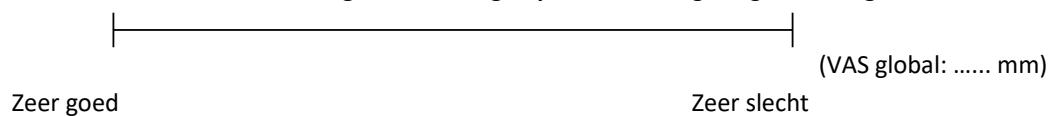
In te vullen door onderzoeker!!

- Wat is uw indruk van de toestand van de patient?

|⊢————————————————————————|

(VAS onderzoeker: …... mm)

Zeer goed   Zeer slecht

45
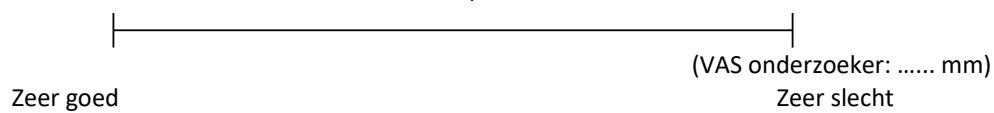
APPENDIX D CARDIOVASCULAR DISEASE QUESTIONNAIRE

1) Hypertensie:	☐Ja	☐Nee
	Behandeling: _____	

2) Hypercholesterolemie:	☐Ja	☐Nee
	Behandeling: _____	

3) Coronairlijden:	☐Zeker	☐Waarschijnlijk
	☐Mogelijk	☐Nee

4) Gedocumenteerd Myocard Infarct?	☐Ja	☐Nee
	Datum: ☐☐-☐☐-☐☐☐☐ (dd-mm-jjjj)	

5) CABG:	☐Ja	☐Nee
	Datum: ☐☐-☐☐-☐☐☐☐ (dd-mm-jjjj)	

6) Angina pectoris:	☐Zeker	☐Waarschijnlijk
	☐Mogelijk	☐Nee
Start van de klachten :	☐☐-☐☐-☐☐☐☐ (dd-mm-jjjj)	

Diagnose AP gesteld n.a.v.	☐(inspannings) ECG	☐CAG
	☐cardioloog	
	☐anders, nl.,_____	

7) Decompensatio cordis:	☐Zeker	☐Waarschijnlijk
	☐Mogelijk	☐Nee
Start van de klachten:	☐☐-☐☐-☐☐☐☐(dd-mm-jjjj)	

Diagnose DC gesteld n.a.v.	☐(inspannings) ECG	☐CAG
	☐cardioloog	
	☐anders, nl.,_____	

8) Cerebrovasculair lijden:	☐Zeker	☐Waarschijnlijk
	☐Mogelijk	☐Nee

9) Gedocumenteerde TIA?	☐Ja	☐Nee

10) Gedocumenteerde CVA?	☐Ja	☐Nee

11) Carotis-endarteriëctomie/ angioplastiek:	☐Ja	☐Nee
	Datum: ☐☐-☐☐-☐☐☐☐(dd-mm-jjjj)	

46

12) Perifeer arterieel vaatlijden: ☐Zeker ☐Waarschijnlijk

☐Mogelijk ☐Nee

13) Claudicatio intermittens klachten: ☐Ja ☐Nee

14) Perifere arteriële vaatreconstructie: ☐Ja ☐Nee

15) Onderbeenamputatie: ☐Ja ☐Nee

16) Heeft of had u een eerste graad familielid die een hartaanval gehad heeft of die bij inspanning een pilletje onder de tong moest gebruiken?

☐Ja ☐Nee

17) Hoe oud was het familielid ongeveer toen deze gezondheidsproblemen begonnen?

☐☐☐jaar

18) Heeft of had u een eerste graad familielid die een beroerte (hersenbloeding, herseninfarct, CVA of TIA) heeft doorgemaakt? ☐Ja ☐Nee

19) Hoe oud was het familielid ongeveer toen hij of zij (voor het eerst) een beroerte doormaakt?

☐☐☐jaar

20) Heeft of had u een eerste graad familielid die last heeft of had van etalagebenen (claudicatio intermittens)? ☐Ja ☐Nee

21) Hoe oud was het familielid ongeveer toen hij of zij voor het eerst last kreeg van deze etalagebenen? ☐☐☐jaar

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APPENDIX E HEALTH ASSESSMENT QUESTIONNAIRE

Nederlandse Consensus Health Assessment Questionnaire

Naam _____ Datum _____

Wij zijn geïnteresseerd in hoe uw ziekte van invloed is op uw functioneren in het dagelijks leven.
U kunt eventueel commentaar toevoegen op de achterzijde van dit papier.

🗙 **Kruis het antwoord aan dat het best beschrijft wat u meestal kon doen IN DE AFGELOPEN WEEK.**

	Zonder ENIGE moeite [0]	Met ENIGE moeite [1]	Met VEEL moeite [2]	ONMOGELIJK uit te voeren [3]	Niet invullen hoogste score
AANKLEDEN & VERZORGING					
Kunt u: —Uzelf aankleden, inclusief veters strikken en knopen dichtmaken?	❏	❏	❏	❏	
—Uw haar wassen?	❏	❏	❏	❏	
OPSTAAN					
Kunt u: —Opstaan vanuit een rechte stoel?	❏	❏	❏	❏	
—In en uit bed komen?	❏	❏	❏	❏	
ETEN					
Kunt u: —Vlees snijden?	❏	❏	❏	❏	
—Een vol kopje of glas naar de mond brengen?	❏	❏	❏	❏	
—Een nieuw pak melk openen?	❏	❏	❏	❏	
LOPEN					
Kunt u: —Buitenshuis op vlak terrein wandelen?	❏	❏	❏	❏	
—Vijf traptreden oplopen?	❏	❏	❏	❏	

🗙 **Kruis aan welke HULPMIDDELEN u gewoonlijk gebruikt voor bovenstaande activiteiten:**

subtotaal

❏ Wandelstok   ❏ Rolstoel   ❏ Aangepast bestek
❏ Rollator/Looprekje ❏ Hulpmiddelen, gebruikt bij het aankleden   ❏ Speciale of aangepaste stoel
❏ Krukken   (knopenhaakje, kousenaantrekker,   ❏ Overig (Specificeer):
                          schoenlepel met lange steel, etc.)   _____

hulp

A/V

Op

🗙 **Kruis elke categorie aan waarvoor u gewoonlijk HULP VAN ANDEREN nodig heeft:**

Et

❏ Aankleden/Verzorging   ❏ Opstaan   ❏ Eten   ❏ Lopen

Lo

Ga door op de achterkant

48

Kruis het antwoord aan dat het best beschrijft wat u meestal kon doen IN DE AFGELOPEN WEEK.
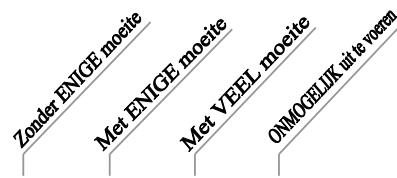
transport

p.1

Niet invullen
Hoogste score

	Zonder ENIGE moeite	Met ENIGE moeite	Met VEEL moeite	ONMOGELIJK uit te voeren
HYGIËNE				
Kunt u: – Zelf Uw lichaam wassen en afdrogen?	❏	❏	❏	❏
– In en uit bad komen?	❏	❏	❏	❏
– Op en van het toilet komen?	❏	❏	❏	❏
REIKEN				
Kunt u: – Iets van ongeveer 2½ kg (bijv. een zak aardappelen of rijst) van net boven uw hoofd pakken?	❏	❏	❏	❏
– Voorover buigen om kleren van de vloer op te rapen?	❏	❏	❏	❏
GRIJPKRACHT				
Kunt u: – Auto–portieren openen?	❏	❏	❏	❏
– Deksels van potjes die al eens geopend zijn, losdraaien?	❏	❏	❏	❏
– Een kraan open– en dichtdraaien?	❏	❏	❏	❏
ACTIVITEITEN				
Kunt u: – Boodschappen doen en winkelen?	❏	❏	❏	❏
– In en uit een auto komen?	❏	❏	❏	❏
– Klusjes doen, zoals stofzuigen of in de tuin werken?	❏	❏	❏	❏

totaal

delen door

Kruis aan welke HULPMIDDELEN u gewoonlijk gebruikt voor bovenstaande activiteiten:

❏ Verhoogd toilet   ❏ Beugels of steunen in badkuip of douche
❏ Douchestoel, douchezitje, badplank   ❏ Hulpmiddelen met lange steel (om ergens bij te kunnen)
❏ Opener voor potten   ❏ Hulpmiddelen met lange steel in de badkamer
   (als de pot al eens geopend is)   ❏ Overig (Specificeer):
_____

ingevulde

categoriën

Kruis elke categorie aan waarvoor u gewoonlijk HULP VAN ANDEREN nodig heeft:

❏ Wassen en toiletbezoek   ❏ Voorwerpen pakken en openen
❏ Naar voorwerpen reiken   ❏ Boodschappen doen en klussen

HAQ-DI

Ruimte voor opmerkingen

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APPENDIX F EUROQOL

Zet bij iedere groep in de lijst hieronder een kruisje in het hokje bij de zin die het beste past bij uw eigen gezondheidstoestand van vandaag.

Mobiliteit
☐ Ik heb geen problemen met lopen
☐ Ik heb enige problemen met lopen
☐ Ik ben bedlegerig

Zelfzorg
☐ Ik heb geen problemen om mijzelf te wassen of aan te kleden
☐ Ik heb enige problemen om mijzelf te wassen of aan te kleden
☐ Ik ben niet in staat mijzelf te wassen of aan te kleden

Dagelijkse activiteiten (bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)
☐ Ik heb geen problemen met mijn dagelijkse activiteiten
☐ Ik heb enige problemen met mijn dagelijkse activiteiten
☐ Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren

Pijn / klachten
☐ Ik heb geen pijn of andere klachten
☐ Ik heb matige pijn of andere klachten
☐ Ik heb zeer ernstige pijn of andere klachten

Stemming
☐ Ik ben niet angstig of somber
☐ Ik ben matig angstig of somber
☐ Ik ben erg angstig of somber

Gezondheid vandaag is vergleken met mijn gezondheid gedurende het afgelopen jaar
☐ beter
☐ ongeveer hetzelfde
☐ slechter

50

Best voorstelbare gezondheidstoestand

Om mensen te helpen bij het aangeven van hoe goed
of slecht een gezondheidstoestand is, hebben we een
meetschaal (te vergelijken met een thermometer)
gemaakt. Op de meetschaal betekent 100 de beste
gezondheidstoestand die men zich kan voorstellen,
en 0 de slechtste gezondheidstoestand die men zich
kan voorstellen.

We willen u vragen op zo'n meetschaal aan te geven
hoe goed of hoe slecht volgens u uw eigen
gezondheidstoestand de afgelopen week is geweest.

Trek nu één lijn van het hokje hieronder naar het punt
op de meetschaal dat volgens u aangeeft hoe goed of

Uw gezondheids-toestand
vandaag

100

90

80

70

60

50

40

30

20

10

0

51
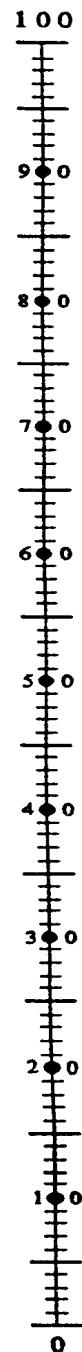
APPENDIX G ARTHRALGIA QUESTIONNAIRE

Studienr. _____

Datum _____

T nr. _____

Achternaam: _____

Voorletters: _____

Vragenlijst:

Symptomen bij personen met een verhoogd risico op reumatoïde artritis

Drs. M.H. van Beers-Tas
Drs. S.A. Turk
Dr. Ir. L.H.D. van Tuyl
Dr. D. Schaardenburg

Reade, centrum voor revalidatie en reumatologie
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Vragenlijst: Symptomen bij personen met een verhoogd risico op reumatoïde artritis

Mogelijk heeft u één of meer van de volgende symptomen ervaren in relatie tot uw huidige periode van gewrichtsproblemen. Wij vragen u om van onderstaande klachten aan te geven van welke u last heeft gehad, en wanneer zij voor het eerst zijn opgetreden. Bijvoorbeeld, wanneer u de laatste 3 maanden gewrichtspijn heeft gehad, en gewrichtszwelling de laatste 4 jaar, maar nooit gewrichtsstijfheid, vult u in:

Voorbeeld van mogelijke klacht	Doorgemaakt (verleden of huidig)	Indien ja, hoe lang geleden is het voor het eerst opgetreden?
Gewrichtspijn	verleden/ huidig / nooit	3 maanden/ jaar
Gewrichtszwelling	verleden/ huidig / nooit	4 maanden/ jaar
Stijfheid van de gewrichten	verleden/ huidig / nooit	… maanden/ jaar

In de onderste twee rijen is er de mogelijkheid om andere klachten toe te voegen, die niet genoemd zijn.

Mogelijke klacht	Doorgemaakt (verleden of huidig)	Indien ja, hoe lang geleden is het voor het eerst opgetreden?
Gewrichtspijn	verleden/ huidig / nooit	… maanden/ jaar
Gewrichtszwelling	verleden/ huidig / nooit	… maanden/ jaar
Stijfheid van de gewrichten	verleden/ huidig / nooit	… maanden/ jaar
Brandend gevoel van de gewrichten	verleden/ huidig / nooit	… maanden/ jaar
Tintelend gevoel in de gewrichten	verleden/ huidig / nooit	… maanden/ jaar
Doof gevoel in de gewrichten	verleden/ huidig / nooit	… maanden/ jaar
Verandering van de huidskleur van de gewrichten	verleden/ huidig / nooit	… maanden/ jaar
Spierkrampen	verleden/ huidig / nooit	… maanden/ jaar
Krachtsverlies	verleden/ huidig / nooit	… maanden/ jaar
Vermoeidheid	verleden/ huidig / nooit	… maanden/ jaar
Emotionele klachten (verdrietig, bezorgd, overstuur)	verleden/ huidig / nooit	… maanden/ jaar
Concentratieproblemen	verleden/ huidig / nooit	… maanden/ jaar
Slaapproblemen	verleden/ huidig / nooit	… maanden/ jaar
Andere symptomen, namelijk: _____	verleden/ huidig / nooit	… maanden/ jaar
Andere symptomen, namelijk: _____	verleden/ huidig / nooit	… maanden/ jaar

Wanneer u **voor deze periode van gewrichtsproblemen** andere klachten heeft gehad, waarvan u denkt dat deze relevant zouden kunnen zijn, kunt u deze hieronder omschrijven:

_____

_____

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De antwoorden op onderstaande vragen zullen ons helpen om meer te begrijpen van het type klachten dat u de **laatste maand** heeft doorgemaakt. Denkt u alstublieft niet te lang na over de vragen; het eerste antwoord dat in u opkomt is vaak het beste.

Graag onderstaande vragen goed doorlezen en dan één optie omcirkelen die het beste bij u past, bijvoorbeeld:

Voorbeeldvraag				
a) Hoeveel dagen, in de afgelopen maand, had u pijn in uw gewrichten?	0 dagen	1 tot 5 dagen	6 tot 15 dagen	16 tot 30 dagen

Vraag 1: Gewrichtspijn				
1a) Hoeveel dagen, in de afgelopen maand, had u pijn in uw gewrichten?	0 dagen	1 tot 5 dagen	6 tot 15 dagen	16 tot 30 dagen
1b) In de afgelopen maand, hoeveel last had u van gewrichtspijn?	Geen	Weinig	Matig	Veel
1c) Wat voor invloed had deze gewrichtspijn op uw dagelijks functioneren (zoals werk, huishoudelijke klusjes, kinderen verzorgen, sociale activiteiten)?	Geen invloed	Geringe invloed	Matige invloed	Grote invloed
1d) Welke van de volgende omschrijvingen past het beste bij uw gewrichtspijn?	Brandende pijn	Scherpe of stekende pijn	Zeurende pijn	Ander type pijn, namelijk: _____
1e) Verspringt uw gewrichtspijn naar andere gewrichten?	Nee	Van de armen naar de benen	Van de benen naar de armen	Van de ene kant naar de andere kant

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Vraag 2: Gewrichtszwelling				
2a) Hoeveel dagen, in de afgelopen maand, had u een zwelling in uw gewrichten?	0 dagen (ga door naar vraag 3)	1 tot 5 dagen	6 tot 15 dagen	16 tot 30 dagen
2b) In de afgelopen maand, hoeveel last had u van gewrichtszwelling?	Geen	Weinig	Matig	Veel
2c) Wat voor invloed had deze gewrichtszwelling op uw dagelijks functioneren (zoals werk, huishoudelijke klusjes, kinderen verzorgen, sociale activiteiten)?	Geen invloed	Geringe invloed	Matige invloed	Grote invloed
2d) Waar voelde u deze gewrichtszwelling? (omcirkel alles wat voor u van toepassing is)	Hand: Één Beide	Arm: Één Beide	Voet: Één Beide	Benen: Één Beide

Vraag 3: Stijfheid van de gewrichten				
3a) Hoeveel dagen, in de afgelopen maand, had u last van stijfheid van uw gewrichten?	0 dagen (ga door naar vraag 4)	1 tot 5 dagen	6 tot 15 dagen	16 tot 30 dagen
3b) In de afgelopen maand, hoeveel last had u van stijfheid van uw gewrichten?	Geen	Weinig	Matig	Veel
3c) Indien u last had van stijfheid van de gewrichten 's ochtends bij het opstaan, hoe lang duurde deze stijfheid?	Ik heb geen ochtendstijf-heid	Minder dan één uur: __minuten *	Tussen de één en twee uur	De gehele ochtend
3d) Wat voor invloed heeft deze stijfheid van de gewrichten gehad op uw dagelijks functioneren (zoals werk, huishoudelijke klusjes, kinderen verzorgen, sociale activiteiten)?	Geen invloed	Geringe invloed	Matige invloed	Grote invloed
3e) Waar voelde u deze stijfheid van de gewrichten? (omcirkel alles wat voor u van toepassing is)	Hand: Één Beide	Arm: Één Beide	Voet: Één Beide	Benen: Één Beide

*Graag invullen hoeveel minuten u gemiddeld last had

Vraag 4: Brandend gevoel in de gewrichten				
4a) Hoeveel dagen, in de afgelopen maand, had u last van een brandend gevoel van uw gewrichten?	0 dagen (ga door naar vraag 5)	1 tot 5 dagen	6 tot 15 dagen	16 tot 30 dagen
4b) In de afgelopen maand, hoeveel last had u van het brandende gevoel van uw gewrichten?	Geen	Weinig	Matig	Veel
4c) Wat voor invloed heeft dit brandende gevoel van de gewrichten gehad op uw dagelijks functioneren (zoals werk, huishoudelijke klusjes, kinderen verzorgen, sociale activiteiten)?	Geen invloed	Geringe invloed	Matige invloed	Grote invloed
4d) Waar voelde u dit brandende gevoel van de gewrichten? (omcirkel alles wat voor u van toepassing is)	Hand: Één Beide	Arm: Één Beide	Voet: Één Beide	Benen: Één Beide

Vraag 5: Prikkend of tintelend gevoel in de gewrichten				
5a) Hoeveel dagen, in de afgelopen maand, had u last van een prikkend of tintelend gevoel?	0 dagen (ga door naar vraag 6)	1 tot 5 dagen	6 tot 15 dagen	16 tot 30 dagen
5b) In de afgelopen maand, hoeveel last had u van een prikkend of tintelend gevoel?	Geen	Weinig	Matig	Veel
5c) Wat voor invloed heeft dit prikkende of tintelende gevoel gehad op uw dagelijks functioneren (zoals werk, huishoudelijke klusjes, kinderen verzorgen, sociale activiteiten)?	Geen invloed	Geringe invloed	Matige invloed	Grote invloed
5d) Waar voelde u dit tintelende gevoel? (omcirkel alles wat voor u van toepassing is)	Hand: Één Beide	Arm: Één Beide	Voet: Één Beide	Benen: Één Beide

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Vraag 6: Doof gevoel in de gewrichten				
6a) Hoeveel dagen, in de afgelopen maand, had u last van een doof gevoel?	0 dagen (ga door naar vraag 7)	1 tot 5 dagen	6 tot 15 dagen	16 tot 30 dagen
6b) In de afgelopen maand, hoeveel last had u van een doof gevoel van uw gewrichten?	Geen	Weinig	Matig	Veel
6c) Wat voor invloed heeft dit dove gevoel gehad op uw dagelijks functioneren (zoals werk, huishoudelijke klusjes, kinderen verzorgen, sociale activiteiten)?	Geen invloed	Geringe invloed	Matige invloed	Grote invloed
6d) Waar voelde u dit dove gevoel? (omcirkel alles wat voor u van toepassing is)	Hand: Één Beide	Arm: Één Beide	Voet: Één Beide	Benen: Één Beide

Vraag 7: Verandering in huidskleur van de gewrichten (zoals wanneer de huid er ongewoon rood, blauw, bruin, etc. uit ziet)				
7a) Hoeveel dagen, in de afgelopen maand, had u last van huidverkleuringen van de gewrichten?	0 dagen (ga door naar vraag 8)	1 tot 5 dagen	6 tot 15 dagen	16 tot 30 dagen
7b) In de afgelopen maand, hoeveel last had u van huidverkleuring?	Geen	Weinig	Matig	Veel
7c) Wat voor invloed heeft deze huidverkleuring gehad op uw dagelijks functioneren (zoals werk, huishoudelijke klusjes, kinderen verzorgen, sociale activiteiten)?	Geen invloed	Geringe invloed	Matige invloed	Grote invloed
7d) Waar had u deze huidverkleuring? (omcirkel alles wat voor u van toepassing is)	Hand: Één Beide	Arm: Één Beide	Voet: Één Beide	Benen: Één Beide

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Vraag 8: Spierkrampen				
8a) Hoeveel dagen, in de afgelopen maand, had u last van spierkrampen?	0 dagen (ga door naar vraag 9)	1 tot 5 dagen	6 tot 15 dagen	16 tot 30 dagen
8b) In de afgelopen maand, hoeveel last had u van spierkrampen?	Geen	Weinig	Matig	Veel
8c) Wat voor invloed hadden deze spierkrampen op uw dagelijks functioneren (zoals werk, huishoudelijke klusjes, kinderen verzorgen, sociale activiteiten)?	Geen invloed	Geringe invloed	Matige invloed	Grote invloed
8d) Waar heeft u spierkrampen gehad? (omcirkel alles wat voor u van toepassing is)	Hand: Één Beide	Arm: Één Beide	Voet: Één Beide	Benen: Één Beide

Vraag 9: Krachtsverlies				
9a) Hoeveel dagen, in de afgelopen maand, had u last van krachtsverlies?	0 dagen (ga door naar vraag 10)	1 tot 5 dagen	6 tot 15 dagen	16 tot 30 dagen
9b) In de afgelopen maand, hoeveel last had u van krachtsverlies?	Geen	Weinig	Matig	Veel
9c) Wat voor invloed heeft krachtsverlies gehad op uw dagelijks functioneren (zoals werk, huishoudelijke klusjes, kinderen verzorgen, sociale activiteiten)?	Geen invloed	Geringe invloed	Matige invloed	Grote invloed
9d) Waar had u dit krachtsverlies? (omcirkel alles wat voor u van toepassing is)	Hand: Één Beide	Arm: Één Beide	Voet: Één Beide	Benen: Één Beide

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Vraag 10: Vermoeidheid				
10a) Hoeveel dagen, in de afgelopen maand, had u last van vermoeidheid?	0 dagen (ga door naar vraag 11)	1 tot 5 dagen	6 tot 15 dagen	16 tot 30 dagen
10b) In de afgelopen maand, hoeveel last had u van vermoeidheid?	Geen	Weinig	Matig	Veel
10c) Wat voor invloed heeft deze vermoeidheid gehad op uw dagelijks functioneren (zoals werk, huishoudelijke klusjes, kinderen verzorgen, sociale activiteiten)?	Geen invloed	Geringe invloed	Matige invloed	Grote invloed

Vraag 11: Emotionele klachten (zoals verdrietig, bezorgd, overstuur)				
11a) Hoeveel dagen, in de afgelopen maand, had u last van emotionele klachten?	0 dagen (ga door naar vraag 12)	1 tot 5 dagen	6 tot 15 dagen	16 tot 30 dagen
11b) In de afgelopen maand, hoeveel last had u van emotionele klachten?	Geen	Weinig	Matig	Veel
11c) Wat voor invloed hebben deze emotionele klachten gehad op uw dagelijks functioneren (zoals werk, huishoudelijke klusjes, kinderen verzorgen, sociale activiteiten)?	Geen invloed	Geringe invloed	Matige invloed	Grote invloed

Vraag 12: Concentratieproblemen				
11a) Hoeveel dagen, in de afgelopen maand, had u last gehad van concentratieproblemen?	0 dagen (ga door naar vraag 13)	1 tot 5 dagen	6 tot 15 dagen	16 tot 30 dagen
11b) In de afgelopen maand, hoeveel last had u van concentratieproblemen?	Geen	Weinig	Matig	Veel
11c) Wat voor invloed hebben deze concentratieproblemen op uw dagelijks functioneren (zoals werk, huishoudelijke klusjes, kinderen verzorgen, sociale activiteiten)?	Geen invloed	Geringe invloed	Matige invloed	Grote invloed

| Vraag 13: Slaapproblemen				
11a) Hoeveel dagen, in de afgelopen maand, had u last van slaapproblemen?	0 dagen (ga door naar vraag 14)	1 tot 5 dagen	6 tot 15 dagen	16 tot 30 dagen
11b) In de afgelopen maand, hoeveel last had u van deze slaapproblemen?	Geen	Weinig	Matig	Veel
11c) Wat voor invloed hebben deze slaapproblemen op uw dagelijks functioneren (zoals werk, huishoudelijke klusjes, kinderen verzorgen, sociale activiteiten)?	Geen invloed	Geringe invloed	Matige invloed	Grote invloed

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Vraag 14: Graag op onderstaande schaal aangeven hoeveel pijn u, afgelopen maand, gemiddeld had in elk van de genoemde lichaamsdelen. Graag het cijfer omcirkelen wat het best past bij uw hoeveelheid pijn, waarbij 0 geen pijn betekend, en 3 veel pijn

		Geen	Weinig	Matig	Veel			Geen	Weinig	Matig	Veel
A	Linker vingers	0	1	2	3	I	Rechter vingers	0	1	2	3
B	Linker pols	0	1	2	3	J	Rechter pols	0	1	2	3
C	Linker elleboog	0	1	2	3	K	Rechter elleboog	0	1	2	3
D	Linker schouder	0	1	2	3	L	Rechter schouder	0	1	2	3
E	Linker heup	0	1	2	3	M	Rechter heup	0	1	2	3
F	Linker knie	0	1	2	3	N	Rechter knie	0	1	2	3
G	Linker enkel	0	1	2	3	O	Rechter enkel	0	1	2	3
H	Linker tenen	0	1	2	3	P	Rechter tenen	0	1	2	3
Q	Nek	0	1	2	3	R	Rug	0	1	2	3

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Q15: Deze vraag gaat over hoe uw klachten zich ontwikkeld hebben, sinds de eerste keer dat ze zijn begonnen. Graag één van onderstaande patronen selecteren die het best weergeeft hoe uw klachten zich ontwikkeld hebben. Tussen de tijd dat uw symptomen voor het eerst zijn begonnen en uw huidige klachten, zijn uw klachten:		
	Graag één hokje selecteren dat het best uw klachtenpatroon omschrijft:	
a) *Snel* toegenomen **en daarna constant aanwezig** (zoals de lijn rechts):		
b) *Geleidelijk* toegenomen tot het huidige niveau (zoals de lijn rechts):		
c) Met **pieken en dalen** toenemend en afnemend, maar *altijd* blijven er *klachten aanwezig* (zoals de lijn rechts):		
d) Met **pieken en dalen**, waarin er periodes zijn waarin u geheel *klachtenvrij* bent (zoals de lijn rechts):		
e) Wanneer bovenstaande patronen niet overeenkomen met uw klachtenpatroon, graag in de ruimte rechts uw klachtenpatroon tekenen, zoals u uw klachten vanaf het begin tot nu heeft doorgemaakt, of beschrijf uw klachtenpatroon hieronder: _____ _____ _____		
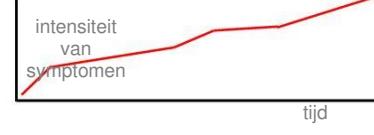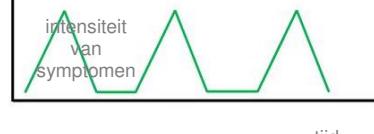
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APPENDIX H CARDIOVASCULAIR RISK TABLE

Tabel 1. Risicotabel: 10-jaarsrisico op ziekte of sterfte door HVZ voor patiënten zonder HVZ

		Vrouwen										Leeftijd	Mannen									
		Niet-rookster					Rookster						Niet-roker					Roker				
Leeftijd	SBD	4	5	6	7	8	4	5	6	7	8		4	5	6	7	8	4	5	6	7	8
70	180	35	38	41	43	44	47	50	>50	>50	>50		>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
70	160	28	31	33	35	36	38	41	44	46	48		45	48	>50	>50	>50	>50	>50	>50	>50	>50
70	140	22	24	26	28	29	31	33	36	38	39		37	40	42	44	46	49	>50	>50	>50	>50
70	120	18	19	21	22	23	25	27	29	30	32		30	32	34	36	38	40	43	45	48	50
65	180	14	17	20	24	30	27	32	37	45	>50		25	30	36	44	>50	45	>50	>50	>50	>50
65	160	10	12	14	17	21	19	22	27	32	39		18	21	26	32	40	33	39	47	>50	>50
65	140	7	8	10	12	15	14	16	19	23	28		12	15	18	23	29	23	28	34	42	>50
65	120	5	6	7	9	11	10	11	14	17	20		9	11	13	16	21	17	20	24	30	38
60	180	10	12	15	18	23	20	23	28	34	42		22	26	32	40	50	40	48	>50	>50	>50
60	160	7	8	11	13	16	14	17	20	24	30		15	19	23	29	36	29	35	42	>50	>50
60	140	5	6	7	9	12	10	12	14	17	21		11	13	16	20	26	20	25	30	38	47
60	120	4	4	5	7	8	7	8	10	12	15		8	9	12	15	19	14	18	22	27	34
55	180	5	6	8	10	12	10	12	15	18	22		13	16	20	26	32	25	31	38	47	>50
55	160	4	4	5	7	9	7	8	10	13	16		10	12	15	18	23	18	22	27	34	43
55	140	3	3	4	5	6	5	6	7	9	11		7	8	10	13	17	13	16	19	24	31
55	120	2	2	3	3	4	4	4	5	6	8		5	6	7	9	12	9	11	14	17	22
50	180	2	3	4	5	6	5	6	7	9	11		8	10	12	15	20	15	18	23	28	36
50	160	2	3	3	3	4	3	4	5	6	8		6	7	9	11	14	11	13	16	20	26
50	140	1	1	2	2	3	2	3	3	4	6		4	5	6	8	10	7	9	12	15	19
50	120	1	1	1	2	2	2	2	2	3	4		3	3	4	6	7	5	7	8	10	13
40	180	1	1	1	1	1	1	1	1	2	2		3	3	4	6	7	5	6	8	10	13
40	160	<1	<1	1	1	1	1	1	1	1	2		2	2	3	4	5	4	4	6	7	9
40	140	<1	<1	<1	1	1	<1	<1	1	1	1		1	2	2	3	4	3	3	4	5	7
40	120	<1	<1	<1	<1	<1	<1	<1	1	1	1		1	1	2	2	3	2	2	3	4	5

Ratio totaal cholesterol/HDL

< 10% risico op ziekte of sterfte door HVZ; leefstijladviezen indien daar aanleiding voor is, zelden medicamenteuze behandeling.

10% tot 20% risico op ziekte of sterfte door HVZ; leefstijladviezen, medicamenteuze behandeling alleen bij risicoverhogende factoren en SBD > 140 mmHg en/of LDL > 2,5 mmol/l.

≥ 20% risico op ziekte of sterfte door HVZ; leefstijladviezen, medicamenteuze behandeling als SBD > 140 mmHg en/of LDL > 2,5 mmol/l.

Het risico bij patiënten met DM of RA kan worden geschat door bij de actuele leeftijd van de patiënt 15 jaar op te tellen.