RESEARCH PROTOCOL

PLANTS FOR JOINTS

Three randomized controlled trials with a one-year extension period on the effect of a multidisciplinary lifestyle program for
(1) patients with rheumatoid arthritis,
(2) patients with ACPA positive arthralgia and
(3) patients with osteoarthritis & metabolic syndrome

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
ACR	**American college of rheumatology**
AE	**Adverse Event**
ACPA	**Anti-citrullinated protein antibody**
AR	**Adverse Reaction**
BMR	**Base metabolic rate**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DAS28	**Disease Activity Score of 28 joints**
DEXA	**Dual-energy X-ray absorptiometry**
DMARD	**Disease modifying anti rheumatic drug**
DSMB	**Data Safety Monitoring Board**
ESR	**Erythrocyte sedimentation rate**
EU	**European Union**
EULAR	**European league against rheumatism**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GUG-test	**Get-up-and-go-test**
HDL	**High density lipoprotein**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IgM-RF	**Immunoglobulin M rheumatoid factor**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
LDL	**Low density lipoprotein**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
MetS	**Metabolic syndrome**
MRI	**Magnetic resonance imaging**
OA	**Osteoarthritis**
PAL	**Physical activity level**

PROMIS®	**Patient Reported Outcome Measures**
RA	**Rheumatoid arthritis**
RCT	**Randomized controlled trial**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WFPD	**Whole foods plant based diet**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**
WOMAC	**Western Ontario and McMaster Universities Osteoarthritis Index**

SUMMARY

Rationale: An unhealthy lifestyle is associated with a higher risk of chronic diseases and conditions such as rheumatoid arthritis (RA), osteoarthritis (OA) and metabolic syndrome (MetS), with the latter being highly prevalent in OA patients. Low-grade inflammation is often present in people with unhealthy lifestyles and may be a key factor in the pathogenesis of chronic inflammatory diseases. Current treatment of RA and OA mainly consists of medication, exercise therapy and (for OA) weight loss. Combining different types of non-pharmacological therapies such as diet, exercise and stress management has shown synergizing effects in other chronic diseases. Whole foods plant-based diets (WFPDs) have shown promising results for the treatment of both RA and OA but were not yet combined with other lifestyle interventions.

Objective: To investigate the effect of a multidisciplinary lifestyle program, based on a WFPD, exercise and stress management on (1) disease activity in patients with RA, (2) RA-risk score in patients with anti-citrullinated protein antibody (ACPA) positive arthralgia and (3) pain, function and stiffness (WOMAC-score) in patients with OA & MetS. A one-year extension study will investigate continued adherence to lifestyle changes and measure to what extent it is possible to taper drug therapy for RA-patients in (near) remission and OA-patients with less perceived pain.

Study design: Three parallel 16-week randomized single-blind controlled trials (RCT), with the same intervention applied in all RCTs in mixed groups, but with separate analysis and reporting comparing a multidisciplinary lifestyle program with usual care (1) in patients with active RA (n=80); (2) patients with ACPA positive arthralgia (n=16, a pilot study) and (3) in patients with OA & MetS (n=80). The control groups will be placed on a waiting list to receive the intervention after 16 weeks. After completion of the lifestyle program, all patients will be followed in a one-year extension study.

Study population: (1) RA patients with low to moderate disease activity (2.6≤DAS28≤5.1) and no or unchanged DMARD treatment for at least 3 months, (2) arthralgia patients without a history of arthritis, seropositive for ACPA and (3) patients with OA in hip and/or knee & MetS.

Intervention: Personal counselling on diet and exercise, followed by 10 meetings in groups of 15 people with theoretical and practical training on a WFPD, exercise and stress management. The control group receives usual care. During the 16-week program the medication remains unchanged. During the one-year extension program subjects have 2 additional group meetings and – if in (near) remission – medication will be tapered in a standardized manner.

Main study parameters/endpoints: The primary outcomes are: difference in mean change between intervention- and control groups for (1) the DAS28 (for RA patients), (2) the RA-risk score (for ACPA positive arthralgia patients) and (3) the WOMAC score (for OA & MetS patients). For the one-year extension study the change in adherence from 0-12 months is the main endpoint.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participation includes a personal intake with a registered dietician and a physiotherapist, and 10 group meetings in the RCT phase, followed by two group meetings in the extension year. Subjects will undergo 3 measurement visits in the course of the RCT (or 5 if starting in the control group) and 2 measurement visits during the extension year. Blood sampling will stay below 80 ml per measurement. Measurements include: questionnaires, physical exam, low-impact physical exercise tests, blood samples at all visits, heart rate variability (HRV) measurements, dual-energy X-ray absorptiometry (DEXA) scans and indirect calorimetry, stool- and urine samples and MRI of liver and thigh (in a subset).
Given the nature of the intervention, there is no risk associated with participation, since the trial concerns healthy behaviour. Subjects are motivated patients and they may see the intervention as an opportunity rather than a burden. Nonetheless, the program may be experienced as difficult or tough. All patients will receive the intervention, either directly or after a waiting list period.

1. INTRODUCTION AND RATIONALE

General note: this protocol describes three intervention studies. The main reason to combine these studies into one protocol is feasibility: the general rationale is similar and, more importantly, the intervention is the same and can thus be applied in mixed groups of patients. However, the outcome measures, analysis and reporting are separate for the three target groups. Thus, producing one protocol avoids extensive duplication inherent in three separate protocols.

The three target groups are:

1. Patients with rheumatoid arthritis (RA)
2. Patients with anti-citrullinated protein antibodies (ACPA) positive arthralgia
3. Patients with both osteoarthritis (OA) and metabolic syndrome (MetS)

This introduction starts with a general rationale, followed by more specific rationales for RA and ACPA positive arthralgia, OA & MetS, the reasons for choosing a multidisciplinary lifestyle program based on a whole food plant-based diet (WFPD) and concludes with a short background on the role of the microbiome.

1.1 General introduction & rationale

Worldwide life expectancy is rising, but healthy life expectancy cannot keep up (2, 3). The interplay between aging and inflammation (also called *inflammaging*) seems to be related to the development of chronic conditions such as type 2 diabetes, Alzheimer's disease, cardiovascular disease, frailty, sarcopenia, osteoporosis, certain types of cancer, OA and RA (4-6). Many of these diseases or conditions are associated with the MetS, which clusters hyperglycaemia, dyslipidaemia, hypertension and visceral adiposity as vascular risk factors (7) and is likely caused by lifestyle factors such as an unhealthy diet, lack of exercise and stress (8). The genetic contribution to some highly prevalent chronic diseases is calculated at 10-20% (RA: estimated at 16% (9)) and may be lower, since 'unfavourable' genes only confer their maximum effect in an unfavourable environment (10, 11). 70-80% of diseases of affluence are probably preventable by lifestyle improvements (10).

Shared risk factors and more than expected co-occurrence are observed in several diseases that have autoimmune- or inflammatory features, including RA, diabetes types 1 and 2, Crohn's disease, autoimmune thyroid disease, atherosclerosis and multiple

sclerosis. A combined feature of these diseases is the presence of a low-grade inflammation, which may be a prerequisite or facilitator for a breach of immune tolerance and thus a common factor underlying several autoimmune diseases (12). Low-grade inflammation is also linked to MetS, which is often present in patients with obesity, RA, OA, diabetes and/or cardiovascular disease (12, 13). Insulin resistance is a key component of the MetS. It is promoted by a diet rich in energy-dense processed foods of poor nutritional value and a sedentary lifestyle and is characterised by an increase in (especially visceral) adipose tissue and reduced muscle mass (14).

Two of the most prevalent rheumatic diseases in the Netherlands are RA (±235,000 patients) and OA (1.3 million patients). Total medical costs for RA and OA together amount to EUR 1,9 billion a year (2.2% of total healthcare costs in The Netherlands). When societal costs are also taken into account (e.g. sick leave and work disability) the total costs increase to 20 billion euro (15-17), or 3% of the Dutch gross domestic product (GDP).

It is timely and appropriate to study the effects of a multidisciplinary lifestyle program in these diseases. In such a study of (risk for) RA and OA, it is necessary to measure not only the appropriate disease-specific outcome parameters (such as disease activity, pain, function, stiffness, risk score for developing RA and self-reported health), but also the level of adherence to the components of the intervention and lastly, metabolic and other parameters that may mediate the effects of the intervention (e.g. lipid profile, blood glucose, insulin sensitivity, intra-abdominal and intramuscular fat mass, heart rate variability, cortisol), A special role is present for the microbiome, which is further specified in section 1.5.

Life style improvement may have beneficial effects on body composition and fat mass distribution, which can be measured by Dual-Energy X-ray Absorptiometry (DEXA), or magnetic resonance imaging (MRI). A recent MRI study showed decreased subfascial and intramuscular fat and improved insulin sensitivity in type 2 diabetes patients on a WFPD, compared with controls on a conventional diabetes diet (18).

A low heart rate variability (HRV) s associated with a variety of conditions including all cause morbidity and mortality in the general population (19), as well as several immune-mediated inflammatory diseases such as lupus erythematosus, systemic sclerosis, RA and inflammatory bowel disease (20, 21). Physical exercise (22-24), relaxation practices

like meditation and yoga (25-28) and various aspects of diet (29), have been shown to benefit HRV.

Salivary cortisol levels reflect physiologically active free plasma cortisol levels. Job stress and general life stress are associated with an increased cortisol awakening response (CAR, measured in saliva obtained 20-45 minutes after waking up) (30). CAR-levels are associated with psychosocial factors and health and can be used as an objective indicator of (dys)function of the hypothalamic–pituitary–adrenal (HPA) axis in addition to self-reported stress (30).

1.2 Introduction & rationale: rheumatoid arthritis (RA) and ACPA positive arthralgia

The present paradigm of RA treatment is early recognition, before joints are damaged by inflammation, and prompt suppression of inflammation with drug therapy targeted to achieve and maintain remission or low disease activity (31). Despite the success of intensified drug therapies which have led to low rates of joint damage and preservation of function in the majority of cases, there are still unmet needs. 30% of RA patients do not respond to the preferred medication (32), 69% of RA patients are still limited by pain, fatigue and reduced mobility (33) and the mortality gap between RA patients and the general population remains, even in the era of early aggressive treatment (34).

The onset of RA has been linked to environmental factors such as:

- unhealthy dietary behaviour (35).
- obesity (36, 37),
- lack of exercise (38),
- stress (39-41) and
- smoking (estimated to cause 33% of seropositive RA) (42).

Their combined contribution however, is not yet known.

RA is determined by genetic, reproductive and environmental factors (figure 1), of which smoking is the strongest environmental factor (36). The presence of obesity, dyslipidaemia and diabetes type 2 increases the risk of RA and is related to diet. Protective dietary features for RA are high consumption of olive- (n-9 fatty acids) and fish oil (n-3 fatty acids). Intake of vitamin D, antioxidants and trace elements might be protective as well, although evidence is less conclusive (43).

The risk for RA in persons with seropositive arthralgia can be quantified by a risk rule score based on clinical characteristics, symptoms and serology (44). Recently, a test for dominance of B-cell receptor clones even improved the accuracy of arthritis prediction in seropositive arthralgia patients (45).

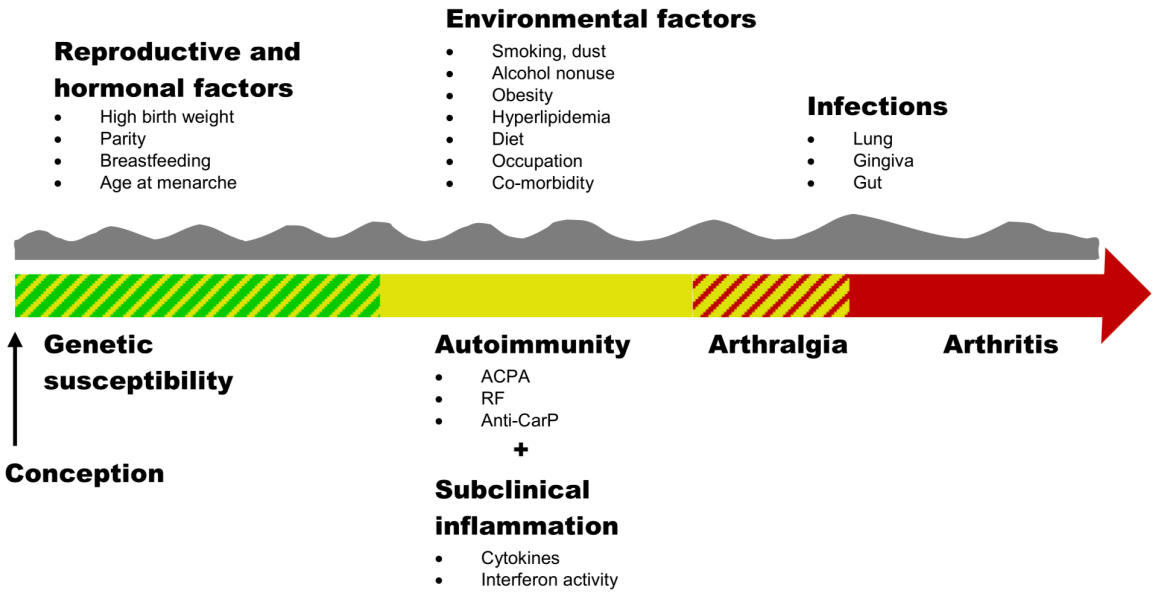

Figure 1: The evolution of RA from health to disease. ACPA, anti–citrullinated protein antibody; RF, rheumatoid factor. anti-CarP, anti-carbamylated protein antibodies (43).

Environmental factors such as diet, physical activity and stress can also influence the course of RA once diagnosed. A systematic review on dietary interventions for RA from 2009 concluded that evidence for the use of Mediterranean or plant-based diets as treatment for RA is limited, mostly due to small size of the trials and risk of bias (46). A one-year randomized controlled (n=53) trial with 7 days of water fasting, a 3-month WFPD, followed by a 9-month vegetarian diet, however, showed significant improvements of all clinical scores (including duration of morning stiffness, number of tender and swollen joints) at 3 months, which was sustained in the following 9 months (47). Another one-year study investigated the effect of a WFPD free of gluten in 66 patients. Of the 22 subjects in the intervention group who completed the study, 9 could be classified as diet-responders based on the ACR20 response criteria, compared with 1 responder in the control group (n=25) (48). But also a shorter, less restrictive intervention in 51 patients, based on a Mediterranean diet low in dairy and meat, showed a significant decrease of the Disease Activity Score 28 (DAS28) and C-reactive protein after 12 weeks (49).

Exercise is related to a 35% lower risk of RA in women in the highest quartile of leisure-time activity (median 40-60 minutes of walking/bicycling a day and median 2-3 hours per week of exercise), compared to the lowest quartile (less than 20 minutes of walking/bicycling a day and less than 1 hour per week of exercise) (38). In established RA, long-term high-intensity exercise is effective in improving functional and emotional status (50). A Cochrane systematic review concluded that aerobic capacity with muscle strength training (similar to the Dutch Exercise Guideline) is recommended as routine practice in patients with RA (51).

Biopsychosocial risk and resilience factors are related to quality of life and disease outcome (figure 2) (1). An extreme example is provided by two studies in about 650,000 veterans and 55,000 nurses showing an increased risk for RA in subjects with post-traumatic stress disorder: in veterans a relative risk of 1.7 (1.4-2.0) and in nurses a hazard ratio of 1.8 (1.2-2.7) (39, 41). Some patients with RA have autonomic dysfunction, which is an imbalance between the parasympathetic and sympathetic nervous system (52), and might be linked to psychopathological conditions (53). RA patients have an increased sympathetic control and decreased parasympathetic control of the heart rate, which results in the finding of a lower heart rate variability (54). A low HRV was already found in patients at increased risk for RA (55)

Reducing stress through Mindfulness Based Stress Reduction (MBSR) showed lower depressive symptoms and psychological distress and improvement of general wellbeing in patients with RA (56). In another one-year study, internet-based cognitive-behavioural

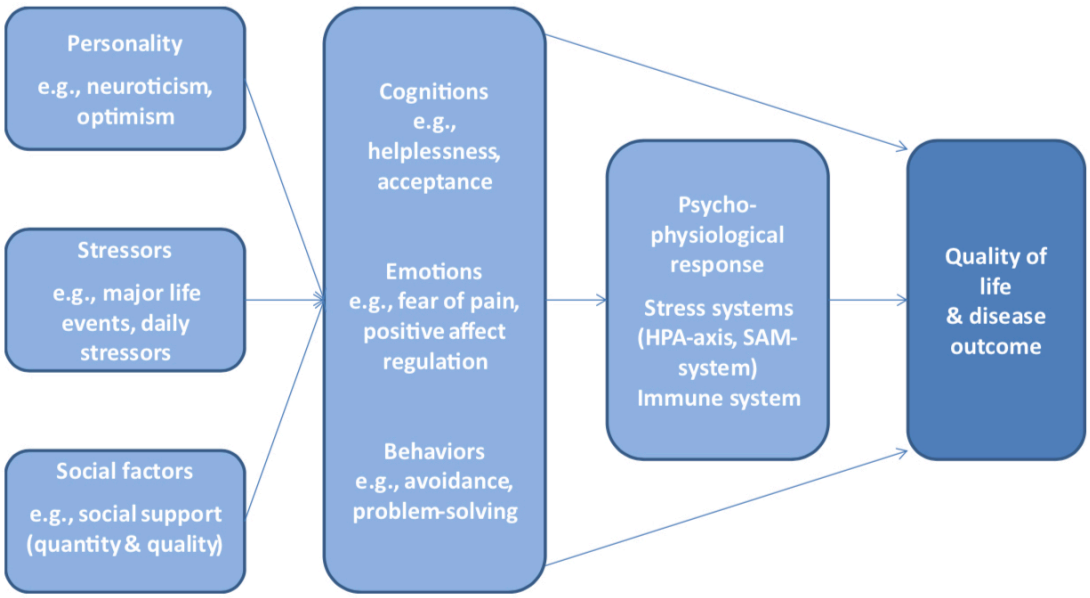

Figure 2: Biopsychosocial adjustment model of risk and resilience factors affecting the quality of life and disease outcome in inflammatory rheumatic diseases (1)

therapy resulted in greater improvements in psychological functioning (depressed and negative mood, anxiety) than standard care, without effects on disease activity (57).

In conclusion, there is evidence that lifestyle factors including diet, exercise and stress have an influence on the risk of developing RA as well as on the course of already diagnosed RA. Interventions based on these life style factors have shown positive effects in established RA, but not yet in persons at risk for RA. In addition, the effect of a multidisciplinary lifestyle intervention, which could have additive or synergistic effects, has not yet been studied in persons with (increased risk for) RA.

1.3 Introduction & rationale: osteoarthritis (OA) & metabolic syndrome (MetS)

The rising prevalence of OA and the obesity epidemic are related (58). Compared to subjects with normal weight, being overweight or obese increased the risk of OA in hand, hip and especially in the knee, and the risk of joint replacement, with a 2-5 fold higher risk for overweight and obese participants (40,41). The higher risk for OA in obese people is related to the increased load on the joints, but also to systemic as well as local inflammation (synovitis) (59).

Having OA was associated with a 5-fold increased risk of MetS according to a US population sample (n=7,714 of which 975 subjects with OA) (60). Levels of inflammatory mediators are higher in people with visceral adiposity, which may mediate the relation between OA and obesity (61) and has resulted in the denomination of metabolic syndrome-associated osteoarthritis (MetS-OA) as a specific form of OA (62).

Treatment of OA comprises analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular glucocorticoids, as well as exercise treatment (muscle strengthening, aerobic activity, adjunctive range of movements and stretching) and mental health (e.g. mood) interventions. The European League Against Rheumatism (EULAR) recommendations for the non-pharmacological management of OA underline the need for weight loss for obese and overweight patients with OA and call for more evidence on *multidisciplinary* approaches, including physiotherapy and exercise, psychological support and dietary advice (63).

Programs including hypocaloric diets for weight loss and exercise have shown to lower pain and improve function in patients with knee OA. This multidisciplinary approach led to superior results when compared with diet-only or exercise-only interventions (64),

suggesting synergies in multidisciplinary interventions. Exercise alone, however, also improves physical function and pain in patients with hip- and/or knee OA (65, 66).

The only published intervention based on a WFPD for patients with OA showed promising results. This 6-week randomized trial (n=37) with OA-patients in which the intervention group (n=19) adhered to a WFPD, resulted in significant weight loss and improved scores on physical functioning, vitality and general health (SF-36) (67). Other interventions showed effectiveness of the WFPD for patients with MetS related diseases (heart disease and diabetes type 2) (68, 69). Weight loss in general (~10%) is associated with less pain and improved function and might be associated with reduced progression of structural damage (70).

Few studies have addressed the effects of stress management techniques (e.g. mindfulness-based stress reduction [MBSR]) for patients with OA. Patients with knee OA and higher baseline 'mindfulness' scores were almost 40% (CI: 1.1-1.8) more likely to respond to exercise than patients with lower baseline mindfulness, with 'acting with awareness' having the greatest magnitude of effect. This suggests that synergies are to be expected when stress management (based on e.g. MBSR-techniques) is used for OA patients who also receive exercise therapy (71).

One pilot study documented the effect of an 8-week meditation program on pain and function. Of the 11 participants, 9 completed the study and showed significant improvements on all core outcomes, such as knee-pain (Western Ontario and McMaster Universities osteoarthritis [WOMAC] -48% ±25%, p=0.001) and function (WOMAC +45% ±30%, p=0,001) (72).

In other chronic diseases, studies have shown independent inverse associations between a whole foods plant based diet (WFPD) (73, 74), exercise and/or less sedentary behaviour (3, 75) and stress management (76) with their incidence and outcomes. Studies on multidisciplinary programs, however, have been limited and where present, focus only on the combination of hypocaloric diets and exercise (64, 77).

1.4 Multidisciplinary lifestyle program based on a WFPD

The unmet needs of RA and OA patients, in combination with the underuse in clinical practice of the present knowledge of environmental risk factors for RA and OA, call for an

increased effort to investigate potentially effective non-pharmacologic options in the treatment of these diseases.

The present protocol is in line with the research agenda in recent EULAR recommendations for the management of RA and OA, to further study non-pharmacological interventions with an emphasis on multidisciplinary treatments, including physiotherapy and exercise, psychological support and dietary advice (63, 78). However, the dietary advice in the recommendations is rather unspecific, mentioning the Mediterranean diet or the need for weight reduction (63, 78).

The Ornish Program (USA, covered by most health insurance companies) is such a multidisciplinary lifestyle program based on a WFPD, exercise and stress management and was shown to be effective in the treatment of coronary heart disease. The program resulted in fewer new cardiac events in the intervention versus the control group (0.9 vs 2.3 events in 5 years/patient, $p<0.001$). 71% (n=20) of the intervention group (n=28) and 75% (n=15) of the control group (n=20) completed 5-year follow-up. Adherence positively influenced the outcome. (69). These results are relevant for our study population, since atherosclerosis and synovitis share pathological features (62, 79) and both RA patients and OA patients with MetS are at increased risk for cardiovascular disease. In spite of these results, and possible effects that the Ornish Program or similar programs could have for other diseases, studies are limited. A WFPD is sometimes considered as too restrictive, which might lead to low adherence. A 6-month study, however, showed that adherence to a WFPD was similar to that of four other less restrictive semi-vegetarian and omnivorous diets, and showed better outcomes for weight, intake of saturated fat and dietary cholesterol intake (80). Studies on the Ornish Lifestyle Program showed good adherence for 5 years, and a 3-month substudy showed equal adherence among four educational levels (69, 81). There is as yet no research on baseline level of motivation among participants.

So far, no study has combined diet, exercise and stress management into one multidisciplinary lifestyle medicine program for patients with (an increased risk for) RA or patients with OA & MetS. Results of studies of a WFPD for both RA and OA patients were promising, but these have not yet been combined with other lifestyle interventions, despite the potential synergies. Therefore, we wish to study the combined effect of a WFPD, exercise and stress management on disease activity (in RA patients), RA-risk score (in ACPA positive arthralgia patients) and pain, function and stiffness (in OA patients). In case the program is effective and there is a need to clarify the specific contribution of the

subparts (e.g. to understand and optimize the effect), future studies can focus on which parts of the program offer the most benefit. An additional advantage of the program is that it can readily be combined with drug therapy as needed.

1.5 The microbiome as possible effect mediator of diet-induced changes in signs and symptoms

The microbiome is the entirety of commensal bacteria populating the skin, oral cavity, upper airways, female genital tract and gut, the gut harboring the largest population. Recent technology has made it possible to study the local bacterial composition in detail. The microbiome appears to have a large influence on health and disease. Although relatively stable, its composition is affected by age, drug use, comorbidity, malnutrition, diet, infections and stress (82).

Several studies, mainly in animals prone to disease, have shed some light on the possible role of the microbiome in the development of inflammatory diseases (82, 83). RA has been shown to be related to periodontal disease. Periodontopathic bacteria stimulate pro-inflammatory cytokine production, such as IL-17 production by T cells, and promote RF and ACPA production (82). Also in the gut, there is evidence of bacterial activity related to RA. Gut-residing *segmented filamentous bacteria* can enhance IL-17 production by upregulating Th17 cells, and have been implicated in the pathogenesis of autoimmune arthritis (84). Other examples are the enrichment of *Lactobacillus salivarius* in the gut of RA patients (related to disease activity in a dose dependent manner) (82) and the enrichment of *Prevotella* species, especially *P. copri*, in the gut microbiota of patients with new-onset RA (85).

Interestingly, autoreactive mouse T cells can be activated by dysbiotic *P. copri* containing fecal transplants from RA patients (86). Subgroups of RA patients have antibodies to *P. copri*, in association with *Prevotella* DNA in synovial fluid, Th17 cytokine responses and ACPA formation, whereas *P. copri* antibodies are rarely found in other rheumatic diseases or healthy controls, suggesting that *P.copri* may cross the intestinal mucosal barrier and is immune-relevant in RA pathogenesis (87).

Regarding OA, obesity and MetS are associated with altered gut microbiota, which could lead to increased gut permeability and the induction of systemic low-grade inflammation through the systemic absorption of intestinal bacterial polymers such as lipopolysaccharide. A diet high in fat and sucrose mimicking the typical Western-type

diet, induced microbiota changes that were highly predictive of high LPS levels and OA in a rat model (88). High fibre diets on the other hand were shown to decrease gut permeability and could therefore play a role in lipopolysaccharide-lowering therapies (89). Modification of the composition of murine gut microbiome by dietary addition of non-digestible carbohydrates (e.g. fibres, readily available in a WFPD), improves gut-barrier integrity and lowers inflammation. Introduction of prebiotic fibre to a high-fat diet specifically increases bifidobacterial numbers and reduces plasma lipopolysaccharide levels, compared with an unsupplemented high-fat diet (89). The anti-inflammatory effect of fibre is also caused by the bacterial production of short chain fatty acids, which promote - among other effects - the differentiation of intestinal T regulatory cells (83). In addition, short chain fatty acids (notably proprionate and butyrate) produced by dietary fibre in mice protect from inflammation-induced bone loss by reducing osteoclast activation while maintaining osteoblast function (90). This may be a relevant factor in secondary osteoporosis of RA patients.

Probiotics, suspensions of beneficial intestinal bacteria, have immunomodulatory effects on B and T cell proliferation and affect cytokine regulation (83). In one study, probiotics were shown to reduce DAS28 and CRP after 8 weeks in RA patients, suggesting a beneficial effect at least in the short term. Diets such as a WFPD can quickly change bacterial diversity and composition, but there are less data on long-term effects (83). More insight on changes in the gut microbiome can be obtained through analyses of the faeces. In addition, recent developments show that more clarification can be given on the effects of these changes through analyses of the metabolites produced by the microbiome. Different diets have shown to result in metabolomic profiles which can be traced back to the macronutrient differences of the diets. The metabolites fall into different categories of which at least one representing metabolites present in food and one formed through microbes in the gastrointestinal tract (91).

In conclusion, there is emerging evidence that the possible benefits of a dietary intervention such as WFPD are mediated in part by an effect on the composition of the oral and/or gut microbiome. Associations between WFPD, clinical effects and alterations in composition of mouth and gut microbiota need to be studied further, and during longer periods.

2. OBJECTIVES

All participants will take part in the lifestyle program in mixed groups and will be followed in a one-year extension study. Objectives, measurements, analyses and reporting are, however, strictly separated in three groups:
(1) RA
(2) OA & MetS
(3) ACPA positive arthralgia

2.1 Objectives rheumatoid arthritis

Primary objective

To investigate the effect of a 16-week multidisciplinary lifestyle program, based on (1) a whole foods plant based diet (WFPD), (2) exercise and (3) stress management;
on disease activity as measured by the disease activity score (DAS28) in patients with RA, in comparison with usual care.

Hypothesis

A 16-week multidisciplinary lifestyle program, based on (1) a WFPD, (2) exercise and (3) stress management
H_0: has no effect on the disease activity in patients with rheumatoid arthritis, in comparison with usual care.
H_1: lowers disease activity in patients with rheumatoid arthritis more than usual care.

Secondary objectives

To investigate the effect of this program on

- quality of life,
- stress (subjective self-reported and biophysical)
- heart rate variability,
- body composition,
- muscle strength,
- muscle mass,
- metabolic syndrome (waist circumference, blood pressure, lipid profile, glucose),
- change in microbiome and metabolome and
- (during the extension period) medication-lowering potential.

2.2 Objectives ACPA-positive arthralgia

Primary objective

To investigate the effect of a 16-week multidisciplinary lifestyle program, based on (1) a WFPD, (2) exercise and (3) stress management;
on the RA-risk score (Amsterdam risk rule score) in patients with ACPA-positive arthralgia, in comparison with usual care.

Hypothesis

A 16-week multidisciplinary lifestyle program, based on (1) a WFPD, (2) exercise and (3) stress management;
H_0: has no effect on the RA-risk score in patients with ACPA-positive arthralgia, in comparison with usual care.
H_1: improves scores of the RA-risk score in patients with ACPA-positive arthralgia, in comparison with usual care.

Secondary objectives

To investigate the effect of this program on

- global health, pain (interference & intensity) and physical function (Dutch-Flemish Patient Reported Outcome Measures (PROMIS®) domains)
- quality of life,
- stress (subjective self-reported and biophysical)
- heart rate variability,
- body composition,
- muscle strength,
- muscle mass and
- metabolic syndrome (waist circumference, blood pressure, lipid profile, glucose),
- change in microbiome and metabolome,
- level of rheumatoid factor and
- level of ACPA
- B-cell receptor clonality

2.3 Objectives osteoarthritis & metabolic syndrome

Primary objective

To investigate the effect of a 16-week multidisciplinary lifestyle program, based on (1) a WFPD, (2) exercise and (3) stress management;
on pain, stiffness and function (combined in the WOMAC index for OA) in patients with hip- and/or knee osteoarthritis and metabolic syndrome, in comparison with usual care.

Hypothesis

A 16-week multidisciplinary lifestyle program, based on (1) a WFPD, (2) exercise and (3) stress management
H_0: has no effect on the WOMAC in patients with hip- and/or knee osteoarthritis and metabolic syndrome, in comparison with usual care.
H_1: lowers the WOMAC (improvement) in patients with hip- and/or knee osteoarthritis and metabolic syndrome, in comparison with usual care.

Secondary objectives

To investigate the effect of this program on

- quality of life,
- stress (subjective self-reported and biophysical)
- body composition,
- muscle strength,
- muscle mass,
- change in microbiome and metabolome and
- metabolic syndrome (waist circumference, blood pressure, lipid profile, glucose).

2.4 One-year extension program

The one-year (12 months) extension program starts after the 16-week intervention. Primary objective of the extension program is to investigate adherence of the participants to program subparts (WFPD, exercise and stress management) as measured by an adapted version of the Lifestyle index adherence score (see paragraph 8.1.1 on main study parameter/endpoint), developed by Ornish et al (92). The above-mentioned objectives will become secondary objectives. In addition, it is the aim to assess the extent to which drug therapy can be tapered in RA patients in (near) remission and OA patients with less perceived pain.

3. STUDY DESIGN

In a 16-week randomized controlled trial (RCT), subjects will either receive usual care or participate in a multidisciplinary lifestyle program based on a WFPD, exercise and stress management. To motivate subjects for this study, all participants will receive the lifestyle program, either directly or after participation in the control group.

Subjects eligible for participation (paragraph 4.2 and 4.3) and who have signed the informed consent, are screened and randomly assigned to the intervention- or the control group. After inclusion the intervention group starts with a personal intake meeting on diet and exercise. Thereafter they will meet ten times in groups of approximately 15 people to work on their lifestyle. They will obtain knowledge on health and lifestyle and gain experience through practical application during the program (e.g. workshops cooking, relaxation exercises and physical training). The waiting list control group will receive usual care as delivered by their rheumatologist and/or general practitioner. See figure 3.

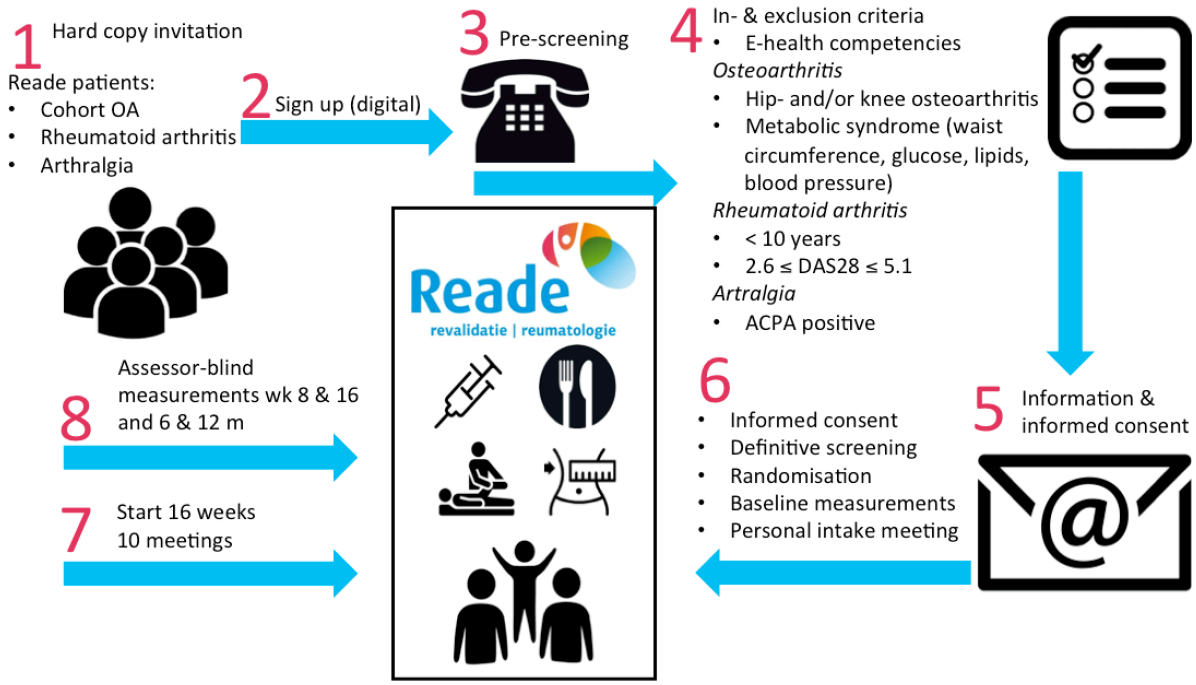

Figure 3: flow chart trial Plants for Joints

Measurements will be taken at baseline, half-way (at 8 weeks) and at conclusion of the 16-week period and in the extension period at 6 and 12 months at Reade (Jan van Breemenstraat). Of all OA patients 30 of 40 participants in the intervention group and 20 of 40 participants in the control group will be invited for an MRI scan at Amsterdam UMC

(location Meibergdreef). Participants can indicate on the Informed Consent form whether or not they want to undergo an MRI scan.

The lifestyle program itself will take place in groups with a maximum of 15 participants per group. All group meetings will take place at Reade, with exception of the first group meeting (more on that in 5. Treatment of subjects).

An overview of the process of this study is presented in figure 4 (see next page).

The design of this unique program is based on earlier studies, but also on the experiences of a group of 15 target group patients ('Ambassadors of Plants for Joints'), who were actively involved in its development. These patients have changed their diet, exercise and/or have implemented stress management techniques, mostly on their own initiative.

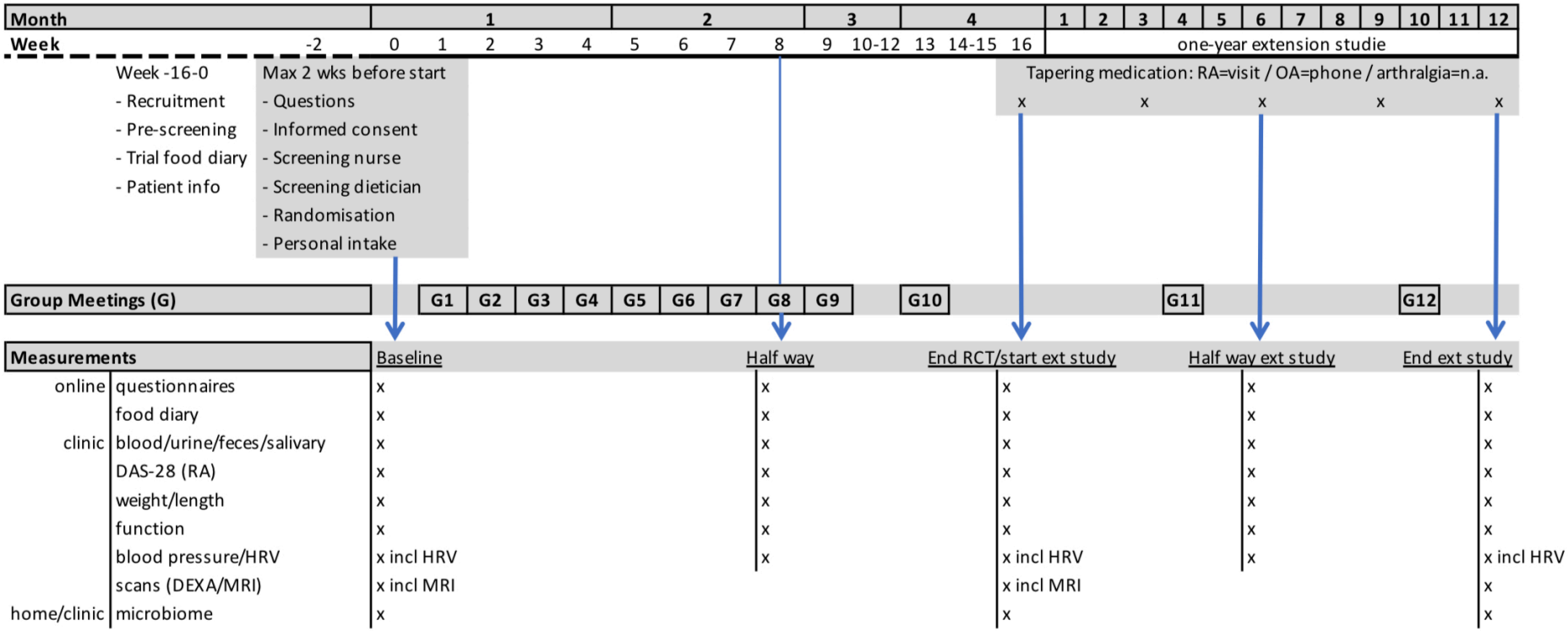

Figure 4: overview process RCT and one-year extension period Plants for Joints. When subjects functioned as control, they will start the lifestyle program after 16 weeks, which makes the maximum duration 20 months (16 weeks control + 16 weeks intervention + 12 months extension study).

4. STUDY POPULATION

4.1 Population (base)

Subjects will be recruited through:

- Rheumatologists, rehabilitation specialists, nurses and paramedics working at Reade, Amsterdam UMC and other hospitals or health centres in the province of Noord-Holland. Presentations will be given to inform doctors and paramedics about the study, and they will be supplied with flyers which can be given to patients. The flyer (see text in appendix A) will forward patients who are interested to the website www.reade.nl/plantsforjoints (see appendix A).
- Reade patients who agreed to be invited for studies, will receive a letter (see text letter in Appendix A) from Reade. This letter guides the interested patient to the website www.reade.nl/plantsforjoints (see appendix A).
- Patients who participated in the Amsterdam Osteoarthritis Cohort (initiated by Reade) and who agreed to be invited for future studies, will receive a letter (see text letter in Appendix A) from Reade. This letter guides the interested patient to the website www.reade.nl/plantsforjoints (see appendix A).
- On the Reade website (www.reade.nl) and through (social) media people are invited to check the information on www.reade.nl/plantsforjoints.

Text outlines are included in appendix A.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

Rheumatoid arthritis:

- Patients ≥ 18 years.
- RA with low to moderate disease activity (2.6≤DAS28≤5.1) according to the EULAR recommendations for use in clinical practice (93).
- Unchanged disease modifying anti rheumatic drug (DMARD) treatment (including unchanged dose) for at least 3 months or non-use of DMARDs, if applicable.

(Clarifying note: patients with at least low disease activity will be included to enable ascertainment of improvement, whereas patients with high disease activity will be

excluded since these patients should receive (a change of medication) according to current guidelines. Recent DMARD changes are an exclusion due to possible confounding effects of slow-acting DMARDs.)

ACPA positive arthralgia:

- Patients ≥ 18 years.
- (History of) arthralgia.
- Seropositive for ACPA.
- No history of arthritis documented by a rheumatologist.

Osteoarthritis & metabolic syndrome:

- Patients ≥ 18 years.
- OA in hip and/or knee, diagnosed according to the clinical criteria or the American College of Rheumatology (without age-criterion) (94, 95):
    - Hip OA: hip pain in combination with either (1) hip internal rotation ≥15º, pain on hip internal rotation and morning stiffness of the hip ≤60 minutes, or (2) hip internal rotation <15º and an ESR ≤ 45 mm/hour (if ESR not available, substitute hip flexion ≤115º).
    - Knee OA: knee pain and 5 (or 3 if no laboratory) of the following criteria: (1) stiffness <30 minutes, (2) crepitus, (3) bony tenderness, (4) bony enlargement, (5) no palpable warmth, (6) ESR <40 mm/hour, (7) RF<1:40, (8) synovial fluid findings of OA.
    - In addition radiography (<2 years, most patients come from an existing cohort study in which radiographs are included) will be used to classify the OA according to the Kellgren-Lawrence grading scheme (96).
- Metabolic syndrome according to the criteria defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) (97): when 3 or more of the following criteria are met: (1) waist circumference ≥102 (♂) / ≥88 (♀) cm, (2) fasting glucose ≥6.1 mmol/l, (3) triglycerides ≥1.7 mmol/l, (4) HDL <1.04 (♂) / <1.29 (♀) mmol/l, (5) blood pressure ≥130/85 mmHg.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study (all three groups):

- Already following a (near-)vegan diet.
- Pregnancy.

- Absolute contra-indication for exercise therapy: resting systolic blood pressure of >200 mmHg or diastolic blood pressure of >115 mmHg, acute myocardial infarction within the last 3 months, chest pain at rest/before exercise, other severe cardiac diseases (e.g. symptomatic aortic stenosis, severe cardiac arrhythmias).
- Underweight (BMI<18,5 kg/m^2).
- In case of smoking, unwillingness to stop smoking for at least the duration of the study.
- Low e-health competencies (lowest proficiency according to Pharos quick scan, see appendix B).
- Insufficient comprehension of Dutch language.
- Inability to be scheduled for therapy or meetings.
- Concurrent presence of other forms of joint disease than OA, RA or ACPA positive arthralgia.
- Psychiatric disease.
- Total arthroplasty of hip or knee scheduled.
- No informed consent.

4.4 Sample size calculation

The study is powered on the primary outcomes DAS28 (or former equivalents), WOMAC pain and WOMAC function (suitable studies did not publish data on WOMAC stiffness scores). Although earlier studies cannot be easily compared with the present one, we used results from vegan, vegetarian and Mediterranean diet and weight loss studies, and studies in which weight loss and exercise were combined (47, 49, 64). Based on α=0.05, power (1-β)=0.80 we found effects ranging from 0.4-0.6 for the DAS28 (RA), 2.2-2.8 for WOMAC pain (OA) and 5.7-10 for WOMAC function (OA) and standard deviations (SD) ranging from 0.6-1.0 for the DAS28, 0.4-0.6 with an exceptional 3.1 for WOMAC pain and 1.4-3.1 with an exceptional 10.9 for WOMAC function.

We made sample size calculations for a one-sided independent samples t-test, and estimated that a power of 0.80 is feasible with a total of 60-70 subjects (intervention + control group) per disease (RA, OA). We plan to include 80 subjects for the RA and OA group each (total 160 patients) based on a possible drop out proportion of approximately 20%.

The study aims for clinically relevant effect sizes (difference in mean change) of Δ0.8 for the DAS28 in RA, Δ1.1 for WOMAC pain and Δ2.8 for WOMAC function in OA (prudently

based on half of the effect achieved in a diet and exercise study (98). Based on scenario analyses with relatively high SDs of 1.2 (DAS28), 0.6 (WOMAC pain) and 3.1 (WOMAC function), an α of 0.05 and a β of 0.2 we reach sample sizes of 56 (RA), 8 (OA, WOMAC pain) and 32 (OA, WOMAC function). Accounting for 20% dropout in the highest needed sample size (n=56), we rounded the sample up to 80 patients per disease.

A subgroup of 50 OA patients will be invited for MRI scans (see 8.1.2 Secondary study parameters/endpoints). We based sample size on earlier studies on changes in visceral adipose tissue (VAT) for patients with overweight, obesity and diabetes type 2 based on diet alone or diet combined with exercise interventions (99-101). Statistically significant and clinically relevant decreases in VAT ranging from 13-29% were found with accompanying sample sizes of 10-60 subjects. A subgroup of 50 patients therefore seems sufficient to detect differences within subjects in time.
For arthralgia (pilot study) the group size will be 16, bringing the total to 176 participants.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The treatment is a lifestyle program, equal for all three intervention groups (RA, OA & MetS and ACPA positive arthralgia patients). After participation in the control group, these subjects will receive the same treatment as the intervention group. During the one-year extension study all participants will be followed during 12 months after the end date of the RCT.

Medication for RA and OA is preferably stable during the lifestyle program (16 weeks for the intervention group, 32 weeks for the control group). When the patient however experiences an RA flare or an increase in pain, analgesics can be increased and medication can be changed after consultation with the rheumatologist.

Any change in medication should be reported to the researcher.

5.1.1 Multidisciplinary lifestyle program

After recruitment patients will be pre-screened (by telephone) to verify eligibility for the study. When patients are considered to be *probably* eligible, they will receive patient information by e-mail. Patients are given at least 1 week to study the patient information and are invited to ask their questions by telephone, e-mail or during the following first visit.

The first visit will start with the definitive screening to verify eligibility. After all questions have been answered and patients are still motivated to join the study, they are requested to sign for informed consent. During the same visit, subjects will be randomized and baseline measurements will be taken. The first visit will be concluded with a personal intake meeting with a registered dietician and a physiotherapist to determine personal objectives (i.e. weight loss), as well as abilities and limitations regarding exercise.

The first visit will take place preferably in week 0 or a maximum of 2 weeks before.

During the 16-week lifestyle program subjects will meet 10 times (weekly from week 1-9 and the last meeting in week 13, with minor rescheduling in case of holidays) in groups of maximum 15 people. Participants are invited to bring their partner/spouse

(or someone else who is able to support the patient in this program) to the first meeting. During all meetings (duration 2- 3 hours) subjects will receive theoretical and/or practical training, based on protocols tested in previous studies on the following topics:

1. Whole foods plant-based diet (e.g. workshops cooking), based on protocols by a.o. Ornish and Barnard (69, 80).
2. Exercise (e.g. brisk walking and/or muscle strengthening exercises), based on the Dutch physical activity guidelines 2017[1] and the protocol by Ornish (69).
3. Stress management (e.g. relaxation exercises), based on protocols by de Brouwer et al. (102).

The program is detailed in appendix C.

Concerning the dietary changes, subjects will be facilitated by means of fully elaborated week plans, cooking class and they will receive a small box with supplements (see paragraph 5.2) and some specific plant-based products (e.g. condiments like miso and nutritional yeast as well as 'cream' substitutes) to get introduced in a new way of cooking. Week plans are made by registered dieticians and are in line with recommended daily allowances (vitamin B12 and D are supplemented according to guidelines, see paragraph 5.2).

The program contains a short 'green fasting' protocol after the first group meeting. This protocol is based on previous research in RA patients showing a decrease in pain, morning stiffness, clinical inflammation and disease activity after a 7-10 day water fasting protocol (47, 49, 103) without adverse effects and with one study showing improvements in morning stiffness and joint tenderness after 2 days of fasting (103). Patients involved in the development of this study strongly recommended to add a fasting protocol. To increase tolerance it is made short and less restrictive (2 days of restriction to green vegetables in the form of salads, juices or blended into smoothies). All patients are recommended to stop fasting as soon as they are not feeling well and to contact the researcher as soon as they have questions.

[1] Dutch Physical Activity Guidelines 2017 by the Health Council of the Netherlands: engage in physical activity of moderate intensity for at least 150 minutes every week, spread over several different days (e.g. walking, cycling), do activities that strengthen muscles and bones at least twice a week and avoid spending long periods sitting down.

Regarding exercise, subjects will be introduced to different forms of moderately intense exercise such as brisk walking, cycling, yoga, fitness, etc. Group practice is focused on moderate exercise, fun and group cohesion. Patients will be motivated to integrate exercise in daily activities (e.g. walk/cycle more rather than sitting in a car or public transport) and verify further possibilities in their direct neighbourhood (experience from an existing module, already in place at Reade called *Sportloket,* will be integrated in the program). Long-term aim for exercise is in line with the Dutch Exercise Guideline: 150 minutes of moderately intense (4,0-6,5 metabolic equivalent of task [MET]) per week with twice a week muscle- and bone-improving activities and less sedentary behaviour (Dutch Exercise Guideline) (104).

With respect to stress management, subjects will receive psycho-education on the effects of stress on health and stress management, as well as guided practice and home exercises (supported by tools, such as audio/Apps) on relaxation techniques (including progressive, cue controlled, and differential relaxation), breathing and visualization exercises and coaching on sleep (102).

A supervisor (one of the involved health professionals) is appointed for every group. The supervisor promotes group cohesion, amongst others by facilitating a digital platform to share experience, meal pictures, questions and progress. The supervisor will also regularly send friendly reminders to enhance adherence to the daily physical and relaxation exercise regime. A total of 2-3 representatives per discipline (total 6-9 professionals) are involved: dieticians, occupational therapists specialized in mindfulness based stress reduction and sleep and physio- or exercise therapists.

5.1.2 One-year extension period

After the 16-week multidisciplinary lifestyle program, subjects are requested to continue to adhere to the lifestyle advice; the intervention is minimalized to two extra group meetings in the 4th and the 10th month during the one-year extension period and measurements will be taken in the 6th and the 12th month by a blinded study nurse (see figure 4).

Medication will be tapered if conditions are met. This will be performed in standardized manner by the research nurse during 3-monthly visits (RA patients) or telephone (OA patients) at 0, 3, 6 and 12 months. The visits in month 6 and 12 will coincide with the measurements. See for a schedule figure 4. Tapering of medication

can be overruled by the treating rheumatologist (with the reason recorded) if considered necessary.

Rheumatoid arthritis

RA patients will visit the rheumatology nurse every 3 months. If in minimal disease activity (DAS<2.6) at any time point, medication will be tapered according to the below schedule. If disease activity increases after tapering, medication will again be increased back to the previous step. Any deviation from the schedule below will be recorded, but otherwise have no consequences.

DMARD Monotherapy

1. Methotrexate (MTX) monotherapy will be adapted according to the following schedule:
    a) The MTX dose will be decreased with 7,5 mg/week per 3 months for dosages between 20-25 mg/week to 10 mg/week followed by step (d) when DAS remains <2.6.
    b) For MTX dose of 17,5 or 15 mg/week, doses will be decreased to 10 mg/week at once followed by step (d) when DAS remains <2.6.
    c) An MTX dose of 12,5 mg/week will be decreased to 7,5 mg mg/week at once followed by step (d) when DAS remains <2.6.
    d) For MTX dosages of 10 or 7,5 mg/week, dosages will be decreased to 5 mg/week at once followed by step (e) when DAS remains <2.6.
    e) MTX can be stopped when the remaining dosage is 5 mg/week and DAS remains <2.6.
2. Leflunomide dose will be decreased with 10 mg/day per 3 months (and stopped, when DAS remains <2.6).
3. Sulfasalazine dose will be decreased with 500 mg/day per 3 months (and stopped, when DAS remains <2.6).
4. Hydroxychloroquine dose will be decreased with 200 mg/d per 3 months (and stopped, when DAS remains <2.6).
5. Prednisone dose ≤7,5 mg/day will be decreased with 2,5 mg/d in a 7-week schedule per 3 months, doses ≥10 mg/day can be decreased at once with 2,5 mg/day per 3 months (and stopped, when DAS remains <2.6).
6. Biological disease-modifying anti-rheumatic drugs (bDMARDs) can be tapered according to the Reade tapering protocol, doubling the interval two times per 3 months and then stopping when DAS remains <2.6.

Combination therapy including bDMARD

The bDMARD is first tapered to stop, followed by a decrease in conventional synthetic DMARDs (csDMARDs) in parallel steps, if more than one type used.

Combination therapy including csDMARD

1. MTX and prednisone: first prednisone is decreased to stop, then MTX.
2. MTX, prednisone, sulfasalazine and hydroxychloroquine: first prednisone is decreased to stop, then sulfasalazine, then hydroxychloroquine and then MTX.
3. With all (other) combination therapy, MTX is tapered as last, except in case of side effects, then MTX is first lowered to a more tolerable dosage.

Additional pain therapy (e.g. paracetamol, tramadol, NSAIDs or morphine) can be tapered according to patient preferences.

Osteoarthritis

OA patients are contacted by the research nurse every 3 months (telephone at 3 and 9 months; visit at 6 and 12 months). Pain therapy is recorded, and patients are stimulated by the research nurse to lower pain therapy (50% every 3 months) when perceived pain is low.

5.2 Use of co-intervention

Not applicable.

5.3 Escape medication

Not applicable.

5.4 Supplementation

During the whole study, subjects will receive vitamin B12 and vitamin D supplementation and they will be advised to continue this supplementation when they decide to continue on a (mostly) plant-based diet after participation.

Vitamin B12 (methylcobalamin)

Vitamin B12 can only be obtained through animal-based foods in the diet or through fortified foods (e.g. plant-based alternatives for milk fortified with vitamin B12). When eating a (mostly) plant based diet, patients should take a supplement for vitamin B12 (105).

In this study subjects will receive 1000 µg/day of methylcobalamin/vitamin B12 (*Vitamine B12 1000 µg* from Vitaminhealth or a comparable supplement, 1 lozenge/day).

Vitamin D3 (cholecalciferol)

High prevalences of vitamin D deficiency (<50 nmol/l) have been reported in the Netherlands (up to almost 60% during wintertime) (106). Vitamin D status depends in part on dietary intake. Since vegetarians and vegans have a lower vitamin D intake, they are more prone to vitamin D deficiency. The US Academy of Nutrition and Dietetics refers to recommendations ranging from 1000 to 2000 international units (IU) (25-50 microgram) a day (105).

In this study subjects receive 50 µg/day (2000 IU) of vitamin D3/cholecalciferol (*Vitamin D3 2000 IU* from Viridian or a comparable supplement, 1 capsule/day).

5.5 Possible adaptations of treatment of comorbidities

Patients with medication for (pre-)diabetes and/or hypertension are instructed to contact their general practitioner and/or their specialist to discuss monitoring lowering of medication when necessary, since blood pressure and blood glucose can decrease in patients who adopt a WFPD. Patients are invited to report changes in medication as soon as possible to the investigators.

6. INVESTIGATIONAL PRODUCT

Not applicable.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

8. METHODS

See Appendix D for a summary and specification of all measurements. For time schedule see figure 4.

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

All measurements will be done at baseline, in week 8 and 16 of the lifestyle program and in the 6th and the 12th month of the one-year extension period, unless otherwise indicated.

RCT rheumatoid arthritis

Main endpoint for RA-patients is the difference between mean change in DAS28 (107) scores from 0-16 weeks (measured blind by a research nurse) in the intervention and control groups.

RCT ACPA positive arthralgia

Main endpoint for the ACPA positive arthralgia-patients is the difference between mean change in RA-risk scores (combined score based on RA prevalence in first degree relatives, alcohol consumption, duration, intermittence and location of symptoms, pain, morning stiffness, swelling of joints and antibody status) (44) from 0-16 weeks in the intervention and control groups.

RCT osteoarthritis & metabolic syndrome

Main endpoint for patients with OA & MetS is the difference between the mean change in the combined scores on pain, stiffness and function, combined in the WOMAC index (108) for OA, from 0-16 weeks in the intervention and control groups.

One-year extension study

Main endpoint for the one-year extension study (all groups) is the change in adherence from 0-12 months, based on an adapted version of the *Lifestyle index adherence score* as developed by Ornish et al (92):

$$\frac{t + ([u / 6 + v / 60] / 2) + ([x / 5 + y / 150] / 2) + z}{4}$$

t = attendance meetings (index, e.g. 0.5 when attended 1 of 2 meetings)
u = stress reduction activities days per week
v = stress reduction activities minutes per week
x = exercise days per week
y = exercise minutes per week
z = adherence to diet
In which z is defined as:

$$\frac{(\text{grams of fibre per 1000 kilocalories}/14) + (10/\text{en\% SFA})}{2}$$

en% SFA = percentage of total kilocalories a day from saturated fatty acids

In the original model by Ornish z was defined by total fat and cholesterol intake. Since our protocol is not based on a low fat WFPD, this definition was not suitable. Therefore, we decided to use fibre and saturated fatty acids (SFAs) as indicators for a WFPD, which can be explained by two characteristics:

- animal based foods do not contain fibres,
- a WFPD is by definition low in SFAs (mostly present in animal-based foods) and
- subjects are motivated to only use whole foods (no processed foods, which contain less or no fibres).

8.1.2 Secondary study parameters/endpoints

Parameters are the same for all groups (RA, OA & MetS and ACPA positive arthralgia) unless otherwise specified.

General

- Self-reported physical (fatigue, pain intensity, pain interference, physical function, sleep disturbance), mental (anxiety, depression) and social (ability to participate in social roles & activities) health using the validated Dutch-Flemish Patient Reported Outcomes Measurement Information System (PROMIS®). This system uses computer adaptive testing (CAT) methods to evaluate physical, mental and social health. With CAT PROMIS® is able the dynamically select items based upon the respondent's previous answers. With this method measurement is limited to 3-7 questions to obtain valid outcomes (109).

Body composition & metabolism

- Body weight (with clothes, no shoes, kg)
- Body height (cm)
- BMI (kg/m2)
- Energy expenditure, measured by indirect calorimetry (Vmax® Encore metabolic cart, CareFusion, Yorba Linda, USA), performed at baseline and at 12 months in the one-year extension study in a fasting state, with at least 20 minutes of rest before measurement and measurement duration of at least 10 minutes, to estimate the resting energy expenditure (110). Energy expenditure is calculated by Weir's formula (111):
  Energy expenditure (kcal) = $3.941 \times VO_2$ (L) + $1.106 \times VCO_2$ (L).
  VO_2 = volume of consumed O_2
  VCO_2 = volume of produced CO_2
- Waist circumference (cm, at approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest).
- Total fat free mass (DEXA, kg & % of body weight)
- Total muscle mass (DEXA, kg & % of body weight)
- Total fat mass (DEXA, kg & % of body weight)
- 50 OA patients (30 from the intervention group and 20 from the control group) will be recruited for MRI examination of:
  - visceral adipose tissue (VAT), spectroscopy will be used to identify fatty acid distribution
  - liver fat content, spectroscopy will be used to identify fatty acid distribution
  - intramuscular fat mass in the thigh muscle
  - synovitis and size of the infrapatellar fat pad, spectroscopy will be used to identify fatty acid distribution

  Based on earlier research small changes seem to occur in 6 months, which is – together with financial motivations – the rationale to use a smaller control group (18). Total time in the MRI scanner is estimated to be maximum 60 minutes.

Physical performance

- Hand grip strength (dynamometer, kg/force), measured as the maximum grip score of 6 trials (3 left, 3 right), with the subject encouraged, in a seated position, forearms rested on the arms of the chair, wrist just over the end of the arm of the chair, in a neutral position, thumb facing upwards, feet flat on the floor, alternating sides (112).
- Function (get-up-and-go test [GUG-test], seconds), measured as the time needed by the subject to get up from a chair without using the hands and to walk as fast as possible to a line 15.2 meters away from the chair (113).
- Physical activity level (PAL, as coefficient related to base metabolic rate [BMR]), measured with a pedometer.

Metabolic

- Blood pressure (mmHg)
- Heart rate variability, performed at baseline, at 4 months and at the end of the extension study. Measured by a 5-minute electrocardiography (ECG) in supine position and a 2-minute ECG during an orthostatic stress test.
- Lipid profile (total cholesterol, LDL, HDL, triglycerides in blood, mmol/l)
- Fasting glucose (blood, mmol/l)
- HbA1c (blood, mmol/mol))

Pathogenesis

- Rheumatoid factor (RF, *ACPA positive arthralgia patients for all measurements, RA patients only at baseline and at the end of the one-year extension study*, blood)
- Anti-citrullinated Protein Antibodies (ACPA, *ACPA positive arthralgia patients for all measurements, RA patients only at baseline and at the end of the one-year extension study*, blood)
- Dominance of B-cell receptor clones (ACPA positive arthralgia patients, at baseline, 4 months and at the end of the extension year)
- Erythrocyte sedimentation rate (ESR, component of DAS28)
- Inflammation in the knee (MRI, categorization)
- Gut microbiota composition (faeces, colony forming units [CFU]/g), collected by the subject at home using an in-house collection kit, frozen, transferred to Reade and brought to -80^{o} C at Reade within 24 hours for later analysis.

- Saliva microbiota composition (saliva, CFU/g), collected by the subject at home using an in-house collection kit, frozen, transferred to Reade and brought to -80^{o} C at Reade within 24 hours for later analysis. A short questionnaire will be used to determine self-reported oral health.
- Metabolome change (blood and urine, percentage change from baseline), collected during measurement visits at Reade and frozen at -80^{o} C for later analysis. Later analysis of microbiome and metabolome samples (including measurement of short chain fatty acids) will be based on the at that time state of the art methods.

8.1.3 Other study parameters

Parameters are the same for all groups unless otherwise specified.

- Smoking (participants are only included in the study when willing to cease smoking for at least the duration of the study)
    - Years smoked
    - Estimated average amount of cigarettes smoked
- Diet (7 consequent days digital diary) at all measurements (during the RCT at baseline, half way and at the end as well as during the extension period at 6 months and 12 months). The diary used is the Dutch 'Eetmeter' by 'Voedingscentrum' (The Netherlands Nutrition Centre), a food diary based on the Dutch food composition database. It is applicable through internet and in the form of an App. Subjects can register online and send their diary to the researchers, who will receive the diary in Excel format. The diary contains per day lists of registered foods, including energy, macro- and micro nutrient content. The following parameters are used and are all averages per day, based on 7-day diaries:
    - Energy intake (kcal/day)
    - Macronutrient intake (grams/day): protein, fats, carbohydrates, fibres and alcohol
    - Micronutrient intake (micro- or milligrams/day): main minerals (calcium, iodine, iron, magnesium, potassium, selenium and zinc) and vitamins (A, B1/thiamine, B2/riboflavin, B3/niacin, B6/pyridoxine, B11/folic acid and B12/cobalamin C, D and E)
- Folic acid (blood, pmol/l)
- Free vitamin B12 (holotranscobalamin in blood, pmol/l)

- Calcidiol (vitamin D/25-OH in blood, nmol/l)
- Haemoglobin (blood, mmol/l)
- Ferritin (blood, µg/l)
- Leukocytes (blood, number of cells/l
- Trombocytes (blood, number of platelets/l)
- Mean corpuscular haemoglobin (MCV, blood, femtolitre)
- Creatinine (blood, µmol/l)
- Alanine transaminase (ALAT, blood, U/l)
- Aspartate transaminase (ASAT, blood, U/l)
- C-reactive protein (CRP, blood, mg/l)
- Cortisol (saliva, nmol/l), collected at 9 a.m. at home using an in-house collection kit, frozen, transferred to Reade and brought to -80^{o} C at Reade within 24 hours for later analysis.

In addition, this study will use a short anonymous digital questionnaire for all patients (including patients who do not wish to continue to participate as part of the pre-screening) as well as health professionals (rheumatologists and other physicians who see target patients regularly, e.g. general practitioners, nurses, physiotherapists, etc) to investigate:

- Patients:
    - Motivation regarding their inquiry or interest in this study.
    - Their current beliefs/opinions on lifestyle and diseases.
    - General information on their current diet, exercise and perceived stress (the perceived stress scale 10 will be used) including possible stress management activities.
    - Reasons for (not) following this program.
    - Opinions on possible effects of diet, exercise and stress management on their health.
    - Opinions on needed research and practical offering of lifestyle programs.
- Health professionals:
    - How often questions are asked by patients on lifestyle, e.g. diet, supplements, exercise, meditation, mental health, smoking, alcohol use, etc.
    - Current ability to answer specific questions on lifestyle and disease.
    - Opinions and expectations on (current) evidence, practical information, programs and future needed research regarding lifestyle and disease.

8.2 Randomisation, blinding and treatment allocation

Patients eligible for the study are randomized by CASTOR (an electronic database platform with strictly defined user roles and patient management procedures) with a 4-8 variable and randomized block list. Subjects will be randomized to the intervention or the control group. Patients in the control group will undergo the study procedures as described in the following paragraph. After their 16-week participation in the control group, members will proceed to the lifestyle program. All participants who have participated in the lifestyle program will join the one-year extension study.

Measurement through blood-, saliva-, faeces- and urine samples, scans, electrocardiography, heart rate variability, digital questionnaires and Apps (food diary) is blinded by definition. A blinded research nurse will perform physical tests and examinations (e.g. get-up-and-go test and DAS28). Patients are instructed (see patient information) to not disclose their allocation to the intervention- or control group during measurements.

8.3 Study procedures

Subjects are requested to answer online questionnaires, to be measured (length, weight, waist circumference, indirect calorimetry and some physical tests) and to keep a food diary (App). The study also requires the collection of saliva, urine and faeces. Blood to be collected for this study will remain below 80 ml per collection at baseline, half-way, at the end of the 16-week intervention period, at the 6th month and at the end of the one-year extension period. Three DEXA scans and (for 50 subjects) two MRI scans are planned. Subjects will be exposed to approximately 0.001 mSv X-ray radiation during each DEXA scan, which is comparable to the amount of naturally occurring background radiation for three hours. All measurements are performed at Reade (dr. Jan van Breemenstraat 2, Amsterdam) with the exception of the MRI scans, which are done at the Amsterdam UMC location AMC (Meibergdreef 9, Amsterdam). See Appendix E and time schedule in figure 4 for a detailed outline of the study procedures.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal

Not applicable.

8.5 Replacement of individual subjects after withdrawal

Subjects will not be replaced after withdrawal.

8.6 Follow-up of subjects withdrawn from treatment

Medical care as needed will be supplied to the subject who discontinues the study. For subjects who discontinue the study due to the occurrence of adverse events potentially related to the intervention, follow-up will take place until the adverse event has abated, or until a stable situation has been reached, with findings being recorded in the CRF. However, given the nature of the intervention, this is not expected.

8.7 Premature termination of the study

Subjects are requested to discontinue participation prematurely when:

- further participation comes with health risks for the patient according to involved medical doctors or other health professionals;
- the subject is unable to follow instructions.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a

period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

Not applicable.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

Not applicable.

10. STATISTICAL ANALYSIS

Descriptive statistics are used for baseline characteristics.

10.1 Primary study parameter(s) for the RCT

Rheumatoid arthritis

At baseline, half-way (8 weeks) and at the end of the study (16 weeks), a blinded nurse (not aware of the allocation of the treatment) will measure the DAS28 (continuous variable). The DAS28 scores at 8 and 16 weeks in the intervention group will be compared with the DAS28 scores at 8 and 16 weeks in the control group, adjusted for baseline DAS28 scores. Intention-to-treat analyses will be performed, with per-protocol analyses as addition. For analysis a repeated measures mixed model with random effect for the subjects and fixed effects for group (intervention or control) and baseline DAS28 values will be used. Two-sided P-values <0.05 will be considered to be significant.

Osteoarthritis & metabolic syndrome

At baseline, half-way (8 weeks) and at the end of the study (16 weeks), subjects will fill out the WOMAC questionnaires (continuous variables). The WOMAC scores at 8 and 16 weeks in the intervention group will be compared with the WOMAC scores at 8 and 16 weeks in the control group, adjusted for baseline WOMAC scores. Intention-to-treat analyses will be performed, with per-protocol analyses as addition. For analysis a repeated measures mixed model with random effect for the subjects and fixed effects for group (intervention or control) and baseline WOMAC scores will be used. Two-sided P-values <0.05 will be considered to be significant.

ACPA positive arthralgia

At baseline, half-way (8 weeks) and at the end of the study (16 weeks), the RA-risk score (continues variable) will be calculated. The RA-risk scores at 8 and 16 weeks in the intervention group will be compared with the RA-risk scores at 8 and 16 weeks in the control group, adjusted for baseline RA-risk scores. Intention-to-treat analyses will be performed, with per-protocol analyses as addition. For analysis a repeated measures mixed model with random effect for the subjects and fixed effects for group (intervention or control) and baseline RA-risk scores will be used. Two-sided P-values <0.05 will be considered to be significant.

10.2 Secondary study parameter(s) for the RCT

At baseline, half-way (8 weeks) and at the end of the study (16 weeks), scores on secondary study parameters (general physical, mental and social health, body composition, physical performance, metabolic parameters, parameters for stress and parameters for disease activity) will be calculated. The scores at 8 and 16 weeks in the intervention group will be compared with the scores at 8 and 16 weeks in the control group, adjusted for baseline scores. Intention-to-treat analyses will be performed, with per-protocol analyses as addition. For analysis a repeated measures mixed model with random effect for the subjects and fixed effects for group (intervention or control) and baseline scores will be used. Since MRI scans will be made only at baseline and at the end of the RCT 16 weeks, regression analysis will be used, with group (intervention versus control) as the independent variable and difference in change from baseline between the groups in MRI data (percentage fat mass in different area's) as the dependent variable. Two-sided P-values <0.05 will be considered to be significant.

10.3 Other study parameters

Descriptive statistics will be used to describe changes in other study parameters.

10.4 Interim analysis

Not applicable.

10.5 Study parameter(s) for the extension study

Adherence is defined in a ratio based on attendance of meetings, diet, exercise and stress management (see formula in paragraph 8.1). The primary and secondary parameters of the intervention study will all become secondary parameters of the extension study and analysed in the same way as during the intervention, using baseline-, halfway- and end measurements during the program, as well as 6 month- and end (12 month) measurements of the extension study. Intention-to-treat analyses will be performed, with per-protocol analyses as addition. Instead of difference between subjects in the intervention- and control group, a within-subject analyses will be performed using a repeated measures mixed model with random effect for the subjects and fixed effects for baseline values. P-values <0.05 will be considered to be significant.

11. ETHICAL CONSIDERATION

11.1 Regulation statement

The study will be conducted in accordance with the principles of the 'World Medical Association Declaration of Helsinki' (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

Subjects will be recruited through:

- Rheumatologists, rehabilitation specialists, nurses and paramedics working at Reade, Amsterdam UMC and other hospitals or health centres in the province of Noord-Holland. Presentations will be given to inform doctors and paramedics about the study, and they will be supplied with flyers which can be given to patients. The flyer (see text in appendix A) will forward patients who are interested to the website www.reade.nl/plantsforjoints (see appendix A).
- Reade patients who agreed to be invited for studies, will receive a letter (see text letter in Appendix A) from Reade. This letter guides the interested patient to the website www.reade.nl/plantsforjoints (see appendix A).
- Patients who participated in the Amsterdam Osteoarthritis Cohort (initiated by Reade) and who agreed to be invited for future studies, will receive a letter (see text letter in Appendix A) from Reade. This letter guides the interested patient to the website www.reade.nl/plantsforjoints (see appendix A).
- On the Reade website (www.reade.nl) and through (social) media people are invited to check the information on www.reade.nl/plantsforjoints.

Prior to study enrolment, written informed consent will be obtained. Participants will get adequate explanation from the investigator(s) or supervising doctors on all details of the study, especially the anticipated benefits and potential risks and the discomfort it may entail. Written informed consent will be obtained prior to screening, with the understanding that consent may be withdrawn at any time without prejudice. Two copies of the informed consent are signed: one is given to the subject and one is retained in the Investigator Site File at the study centre.

11.3 Objection by minors or incapacitated subjects

Not applicable.

11.4 Benefits and risks assessment, group relatedness

We expect no risks of the study procedures and assessments. DEXA/MRI scans and indirect calorimetry are non-invasive and safe but can cause minor discomfort. Blood samples at baseline, half-way and at the end of the trial can also cause minor discomfort. To minimize potential risks of exercise, a physiotherapist will assess each subject individually before inclusion.

Most of the participants will probably benefit from some weight loss. Underweight subjects are excluded.

Subjects will have to invest time and energy in the program but have all the freedom to decide for themselves in how far they are willing to invest in this program. Potential benefits are in line with the objectives of the study: less pain, better functioning and quality of life, weight loss and improvement of other factors related to metabolic syndrome such as improved blood pressure, glucose and lipid profile.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Participants will be compensated for travel expenses (19 eurocents per km) and parking costs.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The data of each subject is stored in an electronic case report form (eCRF) in Castor EDC. Each subject will randomly receive a unique code, produced by Castor EDC. The codes are filed separately and are available to the participating investigators for the duration of the study only. The CRFs will not be disclosed to a third party.

Subjects are informed about data storing and handling and are guaranteed on the discrete handling of their data. Administration of the study will be performed by study investigators and research nurses.

Body material (blood, faeces, urine, saliva) is pseudonymised and stored in the Reade biobank for 15 years. Subjects are asked for permission through the informed consent to use their sample for future research.

As soon as the main analyses have been performed, the patient identification file will be destroyed.

12.2 Monitoring and Quality Assurance

Due to the low risk level of this study, monitoring is not required. To ensure quality of this study the Amsterdam Rheumatology & Immunology Center (ARC) will perform monitoring of source data handling. The monitoring will follow and check the standard operating procedure (SOP) of the Amsterdam UMC, ‘AMC Research Data management SOP’ (May 25 2018, by R.A. Scholte).

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

All amendments will be notified to the METC and to the competent authority.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

This clinical trial will be registered on the website of the 'Nederlands Trial Register', the Dutch member of international public trial registers (http://www.trialregister.nl/trialreg/index.asp) the PhD thesis will be published online, including access to data upon request.

The investigators have the intention to publish the results in a scientific journal.

The METC will be notified of the final start date (date of inclusion of the first subject).

13. STRUCTURED RISK ANALYSIS

Not applicable.

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APPENDIX A: Text outline for mailing, advertisement (print & digital) and website

MAILING/LETTER
Geachte heer, mevrouw,

U ontvangt deze brief, omdat u reuma of artrose heeft. Reade, hét centrum voor reumatologie en revalidatiegeneeskunde in Amsterdam, start binnenkort met een bijzonder wetenschappelijk onderzoek gericht op de verbetering van uw gezondheid. Als u reuma of artrose heeft, dan kunt u misschien meedoen.

In dit wetenschappelijke onderzoek gaat u werken aan uw voedingspatroon, beweging, stress & ontspanning. Het leefstijlprogramma duurt 4 maanden en bestaat uit 10 groepsbijeenkomsten die ruim 2 uur per bijeenkomst duren.

Met dit onderzoek willen wij graag testen of een leefstijlprogramma kan helpen uw gezondheid te verbeteren. Heeft u interesse? Kijk dan op www.reade.nl/plantsforjoints. U kunt daar ook kijken of u geschikt bent om mee te doen.

U kunt ook telefonisch contact opnemen met de betrokken onderzoekers. Bel hiervoor (telefoon 020 242 16 31) of stuur een e-mail, dan nemen wij contact met u op (e-mail: plantsforjoints@reade.nl).

Met vriendelijke groet,

ALGEMEEN/ADVERTENTIE/HOMEPAGE READE/(SOCIAL)MEDIA/FLYER
Reade, hét centrum voor reumatologie en revalidatiegeneeskunde in Amsterdam, start binnenkort met een bijzonder wetenschappelijk onderzoek gericht op de verbetering van uw gezondheid. Als u reuma of artrose heeft, dan kunt u misschien meedoen.

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WEBSITE

Website www.reade.nl/plantsforjoints

Reade, hét centrum voor reumatologie en revalidatiegeneeskunde in Amsterdam, start binnenkort met een bijzonder wetenschappelijk onderzoek gericht op de verbetering van uw gezondheid. Als u reuma of artrose heeft, dan kunt u misschien meedoen.

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<aanvullende informatie over planning/tijden, zodat deelnemers een groep kunnen kiezen met tijden die passend zijn>

Met dit onderzoek willen wij graag testen of een leefstijlprogramma kan helpen uw gezondheid te verbeteren. Aan de hand van de hieronder genoemde criteria, kunt u nagaan of u wellicht in aanmerking komt. Denkt u in aanmerking te komen, dan kunt u uw naam, e-mailadres en telefoonnummer insturen. De onderzoeker neemt dan telefonisch contact met u op. U krijgt daarna nadere informatie per e-mail toegestuurd. Ook wordt er een afspraak met u gemaakt.

Tijdens de afspraak krijgt u nog alle gelegenheid om vragen te stellen en eventueel nog af te zien van deelname. Als u zeker weet dat u mee wilt doen volgt nog een definitieve screening. Pas daarna weet u zeker of u in aanmerking komt voor deelname.

Wij zoeken patiënten met reumatoïde artritis.

- U komt wellicht in aanmerking als u 18 jaar of ouder bent en reumatoïde artritis heeft.
- Als u rookt dan is het belangrijk dat u bereid bent definitief te stoppen voordat u start met het programma.
- Bent u zwanger? Dan kunt u helaas niet meedoen.

Wij zoeken patiënten met artrose in knie- en/of heupgewrichten.

- U komt wellicht in aanmerking als u 18 jaar of ouder bent en artrose heeft in knie- en/of heupgewrichten.
- Als u rookt dan is het belangrijk dat u bereid bent definitief te stoppen voordat u start met het programma.

- Bent u zwanger? Dan kunt u helaas niet meedoen.
- Wij zoeken specifiek naar patiënten met artrose die ook minimaal één van de volgende kenmerken hebben:
    - Een hoge bloeddruk of medicijnen hiervoor.
    - Een verhoogde bloedglucose of medicijnen hiervoor.
    - Een hoog cholesterol of medicijnen hiervoor.

  Stuurt u bij twijfel gerust uw gegevens toe.

<u>Wij zoeken patiënten met een verhoogd risico op reumatoïde artritis.</u>

- U komt wellicht in aanmerking als u 18 jaar of ouder bent, gewrichtsklachten heeft, maar geen gewrichtsontsteking.
- Als u rookt dan is het belangrijk dat u bereid bent definitief te stoppen voordat u start met het programma.
- Bent u zwanger? Dan kunt u helaas niet meedoen.

Ja, ik denk dat ik in aanmerking kan komen voor dit wetenschappelijke onderzoek. Ik wil graag gebeld worden door de onderzoeker.

☐ Ik geef de onderzoeker van Reade toestemming om onderstaande gegevens te gebruiken om met mij contact op te nemen, zodat ik nader geïnformeerd kan worden over dit wetenschappelijke onderzoek.

Voornaam

_____

Achternaam

_____

Telefoonnummer

_____

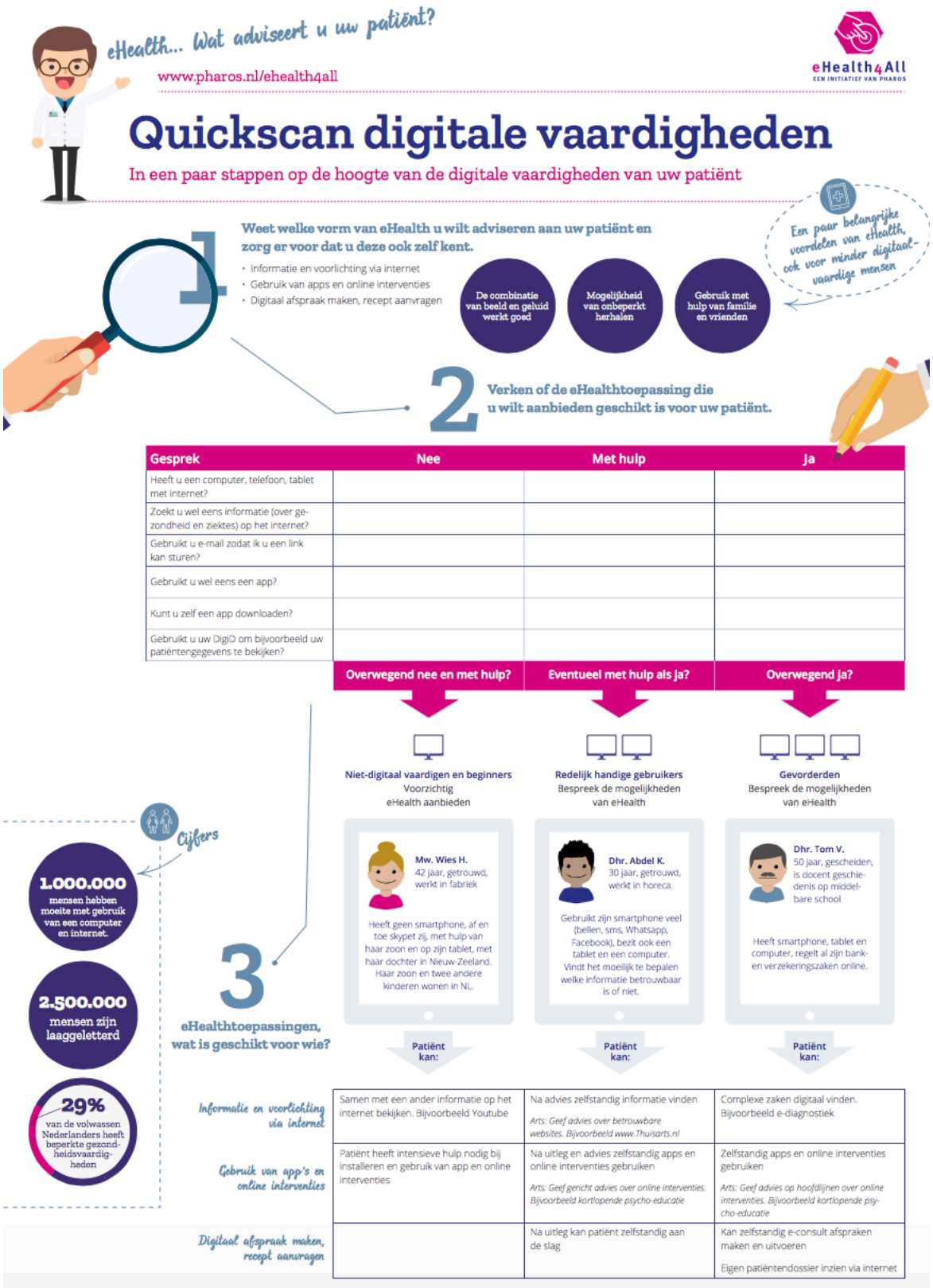
E-mailadres

_____

Klik hier om uw informatie te sturen.

Hartelijk dank voor uw aanmelding. Binnen enkele dagen ontvangt u per e-mail of telefoon nadere informatie of een uitnodiging.

APPENDIX B: Pharox quick scan e-health competencies



APPENDIX C: Plants for Joints Lifestyle Program

Most group meetings (approximately 15 people per group) start with a *roundtable discussion* with the following characteristics:

1. Main focus: diet
2. Group support (sharing successes and failures)
3. Helping each other answering questions (how do you …?) covering subjects as
    - Cooking tips
    - Exercise tips
    - Stress management tips
    - Motivational issues: how to handle myself?
    - Social issues: how to handle situations?

Week	Description
0	Personal intake meeting (physiotherapist & registered dietician)
1	Group meeting Introduction MD Sitting volleyball play (no special clothes needed, breaking down resistance for physical activity) Cooking class with partner/other 'support'
2	Group meeting Roundtable discussion Nutrition theory Introduction stress management, relaxation exercise (bodyscan) and mindful eating/tasting (observation exercise)
3	Group meeting Roundtable discussion Nutrition product knowledge (e.g. reading labels) Why we should be physically active, the downwards spiral (including an exercise on why one is less physically active, awareness) Brisk walking Homework: practicing relaxation during the day, mindful eating and other relaxation exercises (https://www.reade.nl/ontspanning)

4	Group meeting Roundtable discussion (short version, only questions0 Assessing own abilities, body awareness and ‘exercise test’ (to be repeated in week 13) Relaxation & exertion, parasympathetic & sympathetic nervous systems (with exercise to get awareness of these systems) and breathing exercises
5	Group meeting Roundtable discussion Theory physical activity (including physical activity guidelines 2017 by the Health Council of the Netherlands) Physical activity versus exercise and discussion on motivation to stop Homework: relaxation- and breathing exercise (https://www.reade.nl/ontspanning)
6	Group meeting Roundtable discussion Exercise: homework Sleep training (basic education and 'sounder sleep exercise')
7	Group meeting Roundtable discussion The importance of flexibility, body balance, yoga, pilates Homework: relaxation exercise (https://www.reade.nl/ontspanning) and choosing a favourite exercise
8	Group meeting Roundtable discussion Potluck: participants take their most successful recipe Exercise: homework Experience and theory on stress management: how to deal with thoughts (to allow them or not to allow them) and inventory of questions and needs for the 10th group meeting
9	Group meeting Roundtable discussion Basic forms of exercise theory and practical application (coordination, strength, velocity, flexibility and endurance) Homework: relaxation exercise (https://www.reade.nl/ontspanning)

13	Group meeting Roundtable discussion (homework preparation: what makes me (not) maintain my improvements in daily practice?) with celebration of successes Repetition of most important lessons on diet Assessing own abilities, body awareness and ‘exercise test’ (repetition week 4) Answering questions and planning for the time to come. Long relaxation exercise as conclusion

APPENDIX D: Detailed overview of measurements

	Unit	Source	16-week RCT			One-year ext	
			Baseline	Half-way	End	Half-way	End
Main study parameter							
WOMAC (OA)	-	WOMAC	x	x	x	x	x
DAS-28 (RA)	-	Clinical checklist	x	x	x	x	x
RA-risk score (arthralgia)	-	Clinical checklist	x	x	x	x	x
Adherence	-	Formula	x	x	x	x	x
Secondary study parameters							
General questionnaire	-	-	x	x	x	x	x
PROMIS®	-	CAT	x	x	x	x	x
Body weight	kg, clothes no shoes	Scale	x	x	x	x	x
Body height	cm	Stadiometer	x				
BMI	kg/m2	Calculation	x	x	x	x	x
Waist circumference	cm	Tape	x	x	x	x	x
Muscle mass	%body weight	DEXA	x		x		x
Fat mass	%body weight	DEXA	x		x		x
Visceral adipose tissue	% of fat mass	MRI (50 subj)	x		x		
Liver fat content	% of fat mass	MRI (50 subj)	x		x		
Types of fat in liver (e.g. [un]saturated)	% of fat mass/ratio's	MRI (50 subj)	x		x		
Intramuscular fat mass in the thigh muscle	% of fat mass	MRI (50 subj)	x		x		
Types of fat in thigh muscle	% of fat mass/ratio's	MRI (50 subj)	x		x		
Hand grip strength	kg/force	Dynamometer	x		x		x
Function (get-up-and-go-test)	sec	GUG-test	x		x		x
Base metabolic rate (BMR)	kcal/day	Indirect calorimeter	x				x
Physical activity level (PAL)	coefficient/BMR	Pedometer	x	x	x	x	x
Self reported physical/mental/social health	-	PROMIS/CAT	x	x	x	x	x

	Unit	Source	16-week RCT			One-year ext	
			Baseline	Half-way	End	Half-way	End
Blood pressure	mmHg	BP meter	x	x	x	x	x
Heart rate variability		ECG	x		x		x
Lipid profile:	mmol/l	Blood	x	x	x	x	x
LDL							
HDL							
Triglycerides							
n-3 fatty acids							
n-6 fatty acids							
Fasting glucose	mmol/l	Blood	x	x	x	x	x
HbA1c	mmol/mol	Blood	x	x	x	x	x
Erythrocyte sedimentation rate (ESR)	mmol/h	Blood	x	x	x	x	x
C-reactive protein	mg/l	Blood	x	x	x	x	x
IgM-RF (RA & arthralgia)	U/ml	Blood	x	x	x	x	x
Anti-CCP (RA & arthralgia)	U/ml	Blood	x	x	x	x	x
B-cell receptor clones (arthralgia)	%	Blood	x		x		x
CTX-1	pg/ml	Blood	x		x		x
Other study parameters							
Smoking	yes/no	Questionnaire	x	x	x	x	x
Diet (7-day diary):		Eetmeter App	x	x	x	x	x
Energy intake (kcal/day)	kcal/day	-	x	x	x	x	x
Macronutrient intake		Eetmeter App	x	x	x	x	x
Protein	g/kg body weight	-	x	x	x	x	x
Fats	en%	-	x	x	x	x	x
Carbohydrates	en%	-	x	x	x	x	x
Fibres	g	-	x	x	x	x	x

	Unit	Source	16-week RCT			One-year ext	
			Baseline	Half-way	End	Half-way	End
Alcohol	g	-	x	x	x	x	x
Micronutrient intake		Eetmeter App	x	x	x	x	x
Calcium	mg	-	x	x	x	x	x
Iodine	µg	-	x	x	x	x	x
Iron	mg	-	x	x	x	x	x
Magnesium	mg	-	x	x	x	x	x
Potassium	mg	-	x	x	x	x	x
Selenium	µg	-	x	x	x	x	x
Zinc	mg	-	x	x	x	x	x
Vitamin A	µg	-	x	x	x	x	x
Vitamin B1/thiamin	mg	-	x	x	x	x	x
Vitamin B2/riboflavin	mg	-	x	x	x	x	x
Vitamin B3/niacin	mg	-	x	x	x	x	x
Vitamin B6/pyridoxin	mg	-	x	x	x	x	x
Vitamin B11/folic acid	µg	-	x	x	x	x	x
Vitamin B12/cobalamin	µg	-	x	x	x	x	x
Vitamin C/ascoric acid	mg	-	x	x	x	x	x
Vitamin D/cholecalciferol	µg	-	x	x	x	x	x
Vitamin E/tocopherol	mg	-	x	x	x	x	x
Folic acid in plasma	nmol/l	Blood	x	x	x	x	x
Free vitamin B12 (holotranscobalamin)	pmol/l	Blood	x	x	x	x	x
Calcidiol (vitamin D/25-OH)	nmol/l	Blood	x	x	x	x	x
Haemoglobin	mmol/l	Blood	x	x	x	x	x
Leukocytes	nr cells/l	Blood	x	x	x	x	x
Trombocytes	nr platelets/l	Blood	x	x	x	x	x

	Unit	Source	16-week RCT			One-year ext	
			Baseline	Half-way	End	Half-way	End
Mean corpuscular haemoglobin (MCV)	femtolitre	Blood	x	x	x	x	x
Creatinine	µmol/l	Blood	x	x	x	x	x
Alanine transaminase (ALAT)	U/l	Blood	x	x	x	x	x
Aspartate transaminase (ASAT)	U/l	Blood	x	x	x	x	x
Ferritin	µg/l	Blood	x	x	x	x	x
Gut microbiota composition	CFU/g	Feces	x	x	x	x	x
Metabolome	molecules	Blood	x	x	x	x	x
Stored serum	-	Blood	x	x	x	x	x
Salivary cortisol	nmol/l	Saliva	x		x		x
Saliva microbiota composition	CFU/g	Saliva	x	x	x	x	x
Metabolome	molecules	Urine	x	x	x	x	x

APPENDIX E: detailed outline of study procedures

RCT BASELINE MEASUREMENTS			
Before intake (online)	**Tool/method**	**Location**	**Patients**
General questionnaire	-	Online	All
WOMAC	WOMAC	Online	OA
Self reported physical/mental/social health	PROMIS/CAT	Online	All
Intake/baseline measurement: fasting			
Base metabolic rate (BMR)	Indirect calorimeter	Reade	All
Lipid profile (LDL, HDL, triglycerides, n-3/6 fatty acids)	Blood	Reade	All
Fasting glucose	Blood	Reade	All
HbA1c	Blood	Reade	All
Erythrocyte sedimentation rate (ESR)	Blood	Reade	All
C-reactive protein (CRP)	Blood	Reade	All
Rheumatoid factor (IgM-RF)	Blood	Reade	RA & arthralgia
Anti-CCP	Blood	Reade	RA & arthralgia
B-cell receptor clones (arthralgia)	Blood	Reade	arthralgia
CTX-1	Blood	Reade	All
Folic acid in plasma	Blood	Reade	All
Free vitamin B12 (holotranscobalamin)	Blood	Reade	All
Calcidiol (vitamin D/25-OH)	Blood	Reade	All
Haemoglobin	Blood	Reade	All
Leukocytes	Blood	Reade	All
Trombocytes	Blood	Reade	All
Mean corpuscular haemoglobin (MCV)	Blood	Reade	All
Creatinine	Blood	Reade	All
Alanine transaminase (ALAT)	Blood	Reade	All
Aspartate transaminase (ASAT)	Blood	Reade	All
Ferritin	Blood	Reade	All
Metabolome	Blood	Reade	All
Stored serum	Blood	Reade	All
Salivary cortisol	Saliva	Reade	All
Saliva microbiota composition	Saliva	Reade	All
Metabolome	Fasting urine	Pt home	All
Intake/baseline measurement (dietitian / physiotherapist / nurse)			
DAS-28	Nurse (blind)	Reade	RA
RA-risk score	Nurse/researcher	Reade	
Body weight (clothes no shoes)	Scale	Reade	All
Body height	Stadiometer	Reade	All
Waist circumference	Tape	Reade	All
Blood pressure	BP meter	Reade	All
Heart rate variability	5 min ECG	Reade	RA & arthralgia
Hand grip strength	Dynamometer	Reade	All
Function (get-up-and-go-test)	GUG-test	Reade	All
Body composition (muscle/fat mass)	DEXA	Reade	All
Smoking	-	Reade	All
Intake MRI (seperate appointment)			
VAT, liver fat and Intramuscular fat in the thigh muscle	MRI	AMC	50
'Homework' before 1st intervention meeting			
Physical activity level (PAL)	Pedometer	Pt home	All
Diet (7-day diary)	Eetmeter App	Online	All
Gut microbiota composition	Faeces	Pt home	All

RCT HALF-WAY MEASUREMENTS			
'Homework'	**Tool/method**	**Location**	**Patients**
WOMAC	WOMAC	Online	OA
Self reported physical/mental/social health	PROMIS/CAT	Online	All
Physical activity level (PAL)	Pedometer	Pt home	All
Diet (7-day diary)	Eetmeter App	Online	All
Gut microbiota composition	Faeces	Pt home	All
Half-way measurement: fasting			
Lipid profile (LDL, HDL, triglycerides, n-3/6 fatty acids)	Blood	Reade	All
Fasting glucose	Blood	Reade	All
HbA1c	Blood	Reade	All
Erythrocyte sedimentation rate (ESR)	Blood	Reade	All
C-reactive protein (CRP)	Blood	Reade	All
Rheumatoid factor (IgM-RF)	Blood	Reade	Arthralgia
Anti-CCP	Blood	Reade	Arthralgia
Folic acid in plasma	Blood	Reade	All
Free vitamin B12 (holotranscobalamin)	Blood	Reade	All
Calcidiol (vitamin D/25-OH)	Blood	Reade	All
Haemoglobin	Blood	Reade	All
Leukocytes	Blood	Reade	All
Trombocytes	Blood	Reade	All
Mean corpuscular haemoglobin (MCV)	Blood	Reade	All
Creatinine	Blood	Reade	All
Alanine transaminase (ALAT)	Blood	Reade	All
Aspartate transaminase (ASAT)	Blood	Reade	All
Ferritin	Blood	Reade	All
Metabolome	Blood	Reade	All
Stored serum	Blood	Reade	All
Salivary cortisol	Saliva	Reade	All
Saliva microbiota composition	Saliva	Reade	All
Metabolome	Fasting urine	Pt home	All
Half-way measurement (dietitian / physiotherapist / nurse)			
DAS-28	Nurse (blind)	Reade	RA
RA-risk score	Nurse/researcher	Reade	Arthralgia
Body weight (clothes no shoes)	Scale	Reade	All
Waist circumference	Tape	Reade	All
Blood pressure	BP meter	Reade	All
Hand grip strength	Dynamometer	Reade	All
Function (get-up-and-go-test)	GUG-test	Reade	All

RCT END MEASUREMENTS			
'Homework'	**Tool/method**	**Location**	**Patients**
General questionnaire	-	Online	All
WOMAC	WOMAC/CAT	Online	OA
Self reported physical/mental/social health	PROMIS/CAT	Online	All
Physical activity level (PAL)	Pedometer	Pt home	All
Diet (7-day diary)	Eetmeter App	Online	All
Gut microbiota composition	Faeces	Pt home	All
End measurement: fasting			
Lipid profile (LDL, HDL, triglycerides, n-3/6 fatty acids)	Blood	Reade	All
Fasting glucose	Blood	Reade	All
HbA1c	Blood	Reade	All
Erythrocyte sedimentation rate (ESR)	Blood	Reade	All
C-reactive protein (CRP)	Blood	Reade	All
Rheumatoid factor (IgM-RF)	Blood	Reade	Arthralgia
Anti-CCP	Blood	Reade	Arthralgia
B-cell receptor clones (arthralgia)	Blood	Reade	arthralgia
CTX-1	Blood	Reade	All
Folic acid in plasma	Blood	Reade	All
Free vitamin B12 (holotranscobalamin)	Blood	Reade	All
Calcidiol (vitamin D/25-OH)	Blood	Reade	All
Haemoglobin	Blood	Reade	All
Leukocytes	Blood	Reade	All
Trombocytes	Blood	Reade	All
Mean corpuscular haemoglobin (MCV)	Blood	Reade	All
Creatinine	Blood	Reade	All
Alanine transaminase (ALAT)	Blood	Reade	All
Aspartate transaminase (ASAT)	Blood	Reade	All
Ferritin	Blood	Reade	All
Metabolome	Blood	Reade	All
Stored serum	Blood	Reade	All
Salivary cortisol	Saliva	Reade	All
Saliva microbiota composition	Saliva	Reade	All
Metabolome	Fasting urine	Pt home	All
End measurement (dietitian / physiotherapist / nurse)			
DAS-28	Nurse (blind)	Reade	RA
RA-risk score	Nurse/researcher	Reade	Arthralgia
Body weight (clothes no shoes)	Scale	Reade	All
Waist circumference	Tape	Reade	All
Blood pressure	BP meter	Reade	All
Heart rate variability	5 min ECG	Reade	RA & arthralgia
Hand grip strength	Dynamometer	Reade	All
Function (get-up-and-go-test)	GUG-test	Reade	All
Body composition (muscle/fat mass)	DEXA	Reade	All
End MRI (separate appointment)			
VAT, liver fat and Intramuscular fat in the thigh muscle	MRI	AMC	50

ONE-YEAR EXTENSION STUDY: 6 MONTH MEASUREMENT			
'Homework'	**Tool/method**	**Location**	**Patients**
WOMAC	WOMAC	Online	All
Self reported physical/mental/social health	PROMIS/CAT	Online	All
Physical activity level (PAL)	Pedometer	Pt home	All
Diet (7-day diary)	Eetmeter App	Online	All
Gut microbiota composition	Faeces	Pt home	All
Half-way measurement: fasting			
Lipid profile (LDL, HDL, triglycerides, n-3/6 fatty acids)	Blood	Reade	All
Fasting glucose	Blood	Reade	All
HbA1c	Blood	Reade	All
Erythrocyte sedimentation rate (ESR)	Blood	Reade	All
C-reactive protein (CRP)	Blood	Reade	All
Rheumatoid factor (IgM-RF)	Blood	Reade	All
Anti-CCP	Blood	Reade	All
Folic acid in plasma	Blood	Reade	All
Free vitamin B12 (holotranscobalamin)	Blood	Reade	All
Calcidiol (vitamin D/25-OH)	Blood	Reade	All
Haemoglobin	Blood	Reade	All
Leukocytes	Blood	Reade	All
Trombocytes	Blood	Reade	All
Mean corpuscular haemoglobin (MCV)	Blood	Reade	All
Creatinine	Blood	Reade	All
Alanine transaminase (ALAT)	Blood	Reade	All
Aspartate transaminase (ASAT)	Blood	Reade	All
Ferritin	Blood	Reade	All
Metabolome	Blood	Reade	All
Stored serum	Blood	Reade	All
Salivary cortisol	Saliva	Reade	All
Saliva microbiota composition	Saliva	Reade	All
Metabolome	Fasting urine	Pt home	All
Half-way measurement (dietitian / physiotherapist / nurse)			
DAS-28	Nurse (blind)	Reade	RA
RA-risk score	Nurse/researcher	Reade	arthralgia
Body weight (clothes no shoes)	Scale	Reade	All
Waist circumference	Tape	Reade	All
Blood pressure	BP meter	Reade	All
Hand grip strength	Dynamometer	Reade	All
Function (get-up-and-go-test)	GUG-test	Reade	All

ONE-YEAR EXTENSION STUDY: 12 MONTH MEASUREMENT			
'Homework'	**Tool/method**	**Location**	**Patients**
General questionnaire	-	Online	All
WOMAC	WOMAC	Online	All
Self reported physical/mental/social health	PROMIS/CAT	Online	All
Physical activity level (PAL)	Pedometer	Pt home	All
Diet (7-day diary)	Eetmeter App	Online	All
Gut microbiota composition	Faeces	Pt home	All
End measurement: fasting			
Base metabolic rate (BMR)	Indirect calorimeter	Reade	All
Lipid profile (LDL, HDL, triglycerides, n-3/6 fatty acids)	Blood	Reade	All
Fasting glucose	Blood	Reade	All
HbA1c	Blood	Reade	All
Erythrocyte sedimentation rate (ESR)	Blood	Reade	All
C-reactive protein (CRP)	Blood	Reade	All
Rheumatoid factor (IgM-RF)	Blood	Reade	All
Anti-CCP	Blood	Reade	All
B-cell receptor clones (arthralgia)	Blood	Reade	arthralgia
CTX-1	Blood	Reade	All
Folic acid in plasma	Blood	Reade	All
Free vitamin B12 (holotranscobalamin)	Blood	Reade	All
Calcidiol (vitamin D/25-OH)	Blood	Reade	All
Haemoglobin	Blood	Reade	All
Leukocytes	Blood	Reade	All
Trombocytes	Blood	Reade	All
Mean corpuscular haemoglobin (MCV)	Blood	Reade	All
Creatinine	Blood	Reade	All
Alanine transaminase (ALAT)	Blood	Reade	All
Aspartate transaminase (ASAT)	Blood	Reade	All
Ferritin	Blood	Reade	All
Metabolome	Blood	Reade	All
Stored serum	Blood	Reade	All
Salivary cortisol	Saliva	Reade	All
Saliva microbiota composition	Saliva	Reade	All
Metabolome	Fasting urine	Pt home	All
End measurement (dietitian / physiotherapist / nurse)			
DAS-28	Nurse (blind)	Reade	RA
RA-risk score	Nurse/researcher	Reade	
Body weight (clothes no shoes)	Scale	Reade	All
Waist circumference	Tape	Reade	All
Blood pressure	BP meter	Reade	All
Heart rate variability	5 min ECG	Reade	RA & arthralgia
Hand grip strength	Dynamometer	Reade	All
Function (get-up-and-go-test)	GUG-test	Reade	All
Body composition (muscle/fat mass)	DEXA	Reade	All

APPENDIX F: informed consent (separate document PIF)