Does an MRI-guided treatment strategy reduce disease activity and progression in patients with Rheumatoid Arthritis (RA): a randomised controlled trial

The IMAGINE-RA study

Investigator-initiated study

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The project leader is authorised to sign the protocol and protocol amendments for the primary investigator/sponsor.

The protocol relates to the IMAGINE-RA study, which is carried out in accordance with this protocol and the applicable regulatory requirements and legislation in this field.

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Approval of clinical trial protocol

Primary investigator (sponsor): Approval date and signature

30 June
2011

Professor, Consultant Kim Hørslev-Petersen M.D, DMSc

Compliance

All study elements in this protocol, including planning, implementation and reporting are carried out in accordance with applicable national and international legislation and regulations.

1 Background

1. 1 Clinical definition

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease. Patients typically experience pain, functional impairment and reduced quality of life, and are at risk of developing progressive joint damage. The disease primarily affects the small joints of the hands and feet (proximal interphalangeal (PIP) joints, metarcarpophalangeal (MCP) joints, metatarsophalangeal (MTP) joints), but can affect all joints with a synovial membrane. The current treatment strategy involves early and intensive treatment with frequent clinical follow-up, which attempts to control the disease to avoid inflammation and thereby prevent pain, improve function level and avoid joint damage. It is therefore important for optimal treatment of RA patients that methods used for diagnosis, disease monitoring and prognostication are highly sensitive.

Erosive joint damage occurs early in the disease course. Joint destruction is irreversible and causes chronic functional impairment. Early and intensive treatment with inflammation control can slow the destructive disease and prevent function loss [1-3]. However, it has been demonstrated that patients in low disease activity or remission by conventional clinical and biochemical methods still have progressive joint damage [4-6]. This demonstrates that current clinical/biochemical methods used in everyday clinical practice are not sufficiently sensitive and other methods are required for monitoring the disease activity and for prognostication.

The presence of erosions (determined by X-ray examination) as well as anti-cyclic citrullinated peptide (anti-CCP) antibodies and magnetic resonance imaging (MRI) bone marrow oedema (osteitis), are all independent predictors of subsequent radiographic progression [7-13]. Bone marrow oedema has been shown to be the strongest independent predictor in patients with early RA and MRI therefore has significant prognostic value.
It is therefore possible if adding MRI to conventional clinical and laboratory examinations in patients with RA and intensifying treatment if bone marrow oedema is present, will help reduce disease activity, avoid erosive progressive joint damage and prevent function loss.

1.2 Imaging diagnostics

1.2.1. Conventional X-ray examination

Conventional X-ray examination of hands and feet was until the 2010 ACR/EULAR classification criteria[14](Appendix A) part of the classification criteria (1987 ACR classification criteria (Appendix B)), and are used in traditional clinical monitoring of RA patients and in clinical studies. Conventional X-ray examination shows permanent joint damage, such as joint-space narrowing and erosions. The presence of bone erosions early in the disease course is linked to poor radiographic prognosis, progressive joint destruction and a lower function level[17]. Similarly, early erosive progression is linked to lower function level[18]. Erosions shown by conventional X-ray are present in 8-40% of RA patients 6 months after disease onset[19-22] and cannot be used to identify which patients will progress radiographically[23]. Different methods for scoring X-rays have been suggested. The Larsen and Sharp methods and modified versions of these are validated and sensitive to changes, but are time-consuming and not used in everyday clinical practice[26].

1.2.2. Magnetic Resonance Imaging (MRI)

MRI enables 3-dimensional visualisation of all tissue involved in RA (synovial membrane, intra- and extra-articular fluid accumulation, cartilage and bone, bone marrow oedema, ligaments, tendons and tendon sheaths). Optimal visualisation of synovitis requires intravenous administration of contrast agents, which is not the case for bone marrow oedema and erosions[27]. Most RA MRI studies have examined the knee joint and wrists and/or finger joints. MRI shows greater sensitivity in detecting inflammatory and destructive changes than clinical examination and X-ray[28,29]. Comparison of histopathological findings from microarthroscopy and MRI of MCP joints shows good accordance with regard to the presence of erosions and synovitis[30]. Bone marrow oedema, which histologically has shown to be inflammatory infiltrates inside the bone marrow (osteitis)[31,32] has in patients with early RA proved to be the strongest independent predictor of later erosive joint damage progression.[7-13]

Methods used to monitor RA disease activity must be reproducible and sensitive to changes. The OMERACT (Outcome Measures in Rheumatology) initiative has developed a semi-quantitative scoring system RAMRIS (RA MRI scoring system)[33], which has been shown to be sensitive to changes (determined *inter alia* by standardised response mean) and reproducible (good inter- and intra-observer reliability) for the assessment of inflammatory (bone marrow oedema, synovitis) and destructive (erosions) disease manifestations in hands and wrists[34]. RAMRIS is now used internationally in MRI studies of RA patients[35-37].

2 Rationale

It has been shown that early and intensive treatment of RA patients can slow joint damage progression and thereby prevent irreversible function loss. However, current conventional clinical/laboratory and image diagnostic methods used in everyday clinical practice to assess changes in disease activity are not sufficiently sensitive. Patients in low disease activity or in remission, still show progressive erosive joint damage. This indicates that there is a serious need for other methods for monitoring the disease activity and prognostication. Several studies show that MRI is more sensitive in detecting inflammation and destructive changes compared to conventional X-ray and that bone marrow oedema detected by MRI is a strong independent predicator of subsequent joint damage. It is however not known whether treatment intensification based on sub-clinical inflammation, indicated by the presence of MRI-detected bone marrow oedema, in RA patients in low disease activity/remission, will improve clinical and radiographic outcome by reducing erosive joint damage progression, increase the remission rate, prevent pain and function loss, and improve function level.

3 Hypothesis

The current study is based on the following hypothesis:
By adding MRI to conventional clinical and laboratory assessments in RA patients in low disease activity/remission and intensify treatment in case of sub-clinical inflammation (presence of MRI bone marrow oedema), it is possible to prevent erosive joint damage, improve function level, quality of life and increase the remission rate.

4 Objectives

To examine whether an MRI-guided treatment strategy based on a predefined treatment algorithm can prevent progression of erosive joint damage, increase the remission rate and improve function level in the short and long term.

5 Study design

The study is a prospective 2-year multi-center, two-arm, randomised controlled trial (RCT) involving 200 RA patients.
The main inclusion criteria are RA with reference to the ACR/EULAR 2010 RA classification criteria, anti-CCP positivity, erosions detected by conventional X-ray, no swollen joints, DAS28<3.2, unchanged anti-rheumatic treatment ≥6 weeks and no previous biological treatment.

5.1 Randomisation

The patients will be randomised 1:1, into:

Arm A: Treatment algorithm based on conventional biochemical and clinical examinations **or**
Arm B: Treatment algorithm based on conventional biochemical and clinical examinations **and MRI.**

The randomisation and allocation are done electronically in the electronic CRF (e-CRF) at the inclusion visit. The randomization sequence is created by an independent statistician (RC) using a ”random number” generator SAS statistical software (version 9.2.) The randomisation sequence is entered into the e-CRF by an independent data manager (NSK). The participants will be given their study number and randomisation group when the physician ”clicks” on a ”randomisation button”, which only will appear on the screen at the baseline visit if main inclusion criteria are fulfilled after the following are registered in the e-CRF: 0 swollen joints, DAS28-CRP calculated in the system to <3.2. The result of the randomization and the allocated intervention (MRI-guided/not MRI-guided treatment) and the randomization number will hereafter be visible on the screen (e.g. R128). Dependent of the allocated intervention the MRI result (BME present/BME absent), will be visible on the screen (only for patients randomized to MRI-guided treatment). Thus, the patients are given consecutive screening and randomisation numbers, independent of the study site.

5.2 Treatment intensification in the case of unsatisfactory inflammatory activity

Both treatment arms are monitored in accordance with the predefined treatment algorithm (see Section 8.0) and medical treatment is intensified in the case of *”unsatisfactory inflammatory activity”*, defined as the presence of at least one clinically swollen joint (see Section 11.2.2.) and DAS28>3.2 (Arm A and B) **AND/OR** MRI-detected bone marrow oedema score > 0 with reference to OMERACT RAMRIS score (Arm B).

5.3 Clinical and image diagnostic follow-up

Both treatment arms are based on treatment intensification at the scheduled ordinary visits every 4 months, if the treatment target has not been met and the patient is having *unsatisfactory inflammatory activity (see Sections 5.2 and 8.1.2).*

5.3.1 Clinical follow-up
Patients are followed every 4 months (month: 0, 4, 8, 12, 16, 20, 24).
At the ordinary 4-monthly visits, the patients are followed-up clinically and biochemically, including DAS28-CRP, and intra-articular glucocorticoid injection is administered in every clinically swollen joint.

If *unsatisfactory inflammatory activity* occurs between the ordinary 4-monthly visits, a clinical and biochemical examination will be carried out and intra-articular glucocorticoid injection may be administered in clinically swollen joints. Glucocorticoid administration should be avoided if at all possible < 6 weeks prior to the next ordinary 4-monthly visit.

MRI:
MRI of unilateral 2nd to 5th MCP joints and wrist of the dominant hand:

Arm A: Month 0, 12, 24 (the site investigator will not be informed of the result).
Arm B: Month 0, 4, 8, 12, 16, 20, 24 (the site investigator will be informed of the result).

Conventional X-ray examination (X-ray):
Conventional X-ray of hands, wrists and feet:

Arm A and B: Month 0, 12, 24 (the site investigator will not be informed of the result – irrespective of the treatment arm).

After study termination evaluation of X-ray images and MRI scans will be carried out centrally and the readers will be blinded to clinical, biochemical and other image data. The readers are experienced in evaluation with regard to the Sharp/vdHeijde method and the RAMRIS scoring method.

Note: Ultrasonic examination of joints to assess disease activity is NOT permitted.

6 Time schedule

The study is expected to start on 1 September 2011 and the recruitment period is estimated to around 18 months. The last patient is then expected to be enrolled by 1 March 2013 and will have completed the study on 1 March 2015. Data registration will be carried out on an ongoing basis and data analysis is expected to begin in March 2015.

7 Selection of the patient population and selection criteria

Patients are recruited to the trial at the participating centres' outpatient clinics. The centres will ask patients (with known erosive disease described on conventional X-ray, anti-CCP positivity, low disease activity (DAS<3.2)) whether they would consider participating in the study. Oral and written information will be provided. If the patient wishes to participate, a screening visit will be carried out with reference to the trial protocol's inclusion and exclusion criteria. If the patient satisfies the inclusion criteria and none of the exclusion criteria, a declaration of consent and declaration of power of attorney is signed.
Patients will not be recruited through advertising.

7.1 Inclusion criteria

- Age>18 years
- RA with reference to ACR (American College of Rheumatology)/EULAR (European League Against Rheumatism) 2010 criteria.
- Anti-CCP positivity (above the upper normal limit according to local laboratory range)
- Erosions (described by the local radiologist) on conventional X-ray of hands, wrists and/or feet
- No clinically swollen joints (assessed clinically by the site investigator)
- DAS28 (4 variable, CRP) < 3.2
- DMARD monotherapy treatment OR combination treatment, in the form of 2- or 3-drug therapy. If the patient is receiving 3-drug therapy, at least one of the drugs must be administered at less than the "maximum inclusion dose"*
- Unchanged anti-rheumatic treatment in the previous 6 weeks or more
- No previous treatment with biologics
- No contra-indications for TNF-inhibitors
- No contra-indications for MRI
- s-creatinine in normal range
- Ability and willingness to give written and oral informed consent and fulfil the requirements of the study programme with reference to the protocol

* Maximum "inclusion dose" is defined as: MTX 25 mg/week (or maximum tolerated dose if 25 mg/week is not tolerated), SSZ 2g/day (or maximum tolerated dose if 2 g/day is not tolerated) and HCQ 200 mg/day (or maximum tolerated dose if 200 mg/day is not tolerated)

7.2 Exclusion Criteria

- Previous or current biologic treatment
- Known intolerance to methotrexate treatment which means that the patient is not able to tolerate a minimum of MTX 7.5 mg (minimum dose).
- DMARD 3-drug therapy at maximum tolerated/maximum "inclusion dose"*
- Intra muscular, intra-articular or intra venous glucocorticoid administration ≤ 6 weeks prior to inclusion
- Oral glucocorticoid administration > 5 mg/day
- Changes in oral glucocorticoid dose < 3 months prior to inclusion
- Myocrisin treatment

- Affected liver enzymes > 2 x the upper limit of normal at the time of screening
- Current pregnancy or pregnant wish
- Contra-indications for TNF-inhibitors:
    - Active infections or chronic infections requiring treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days of the start of TNF-inhibitors
    - Immunosuppressive condition or HIV infection
    - Active or chronic hepatitis B and/or C virus infection
    - Persons with latent TB (positive Quantiferon test or thorax X-ray examination indicating TB) or other risk factors for activation of latent TB in patients who have not undergone treatment for latent TB in accordance with the treating department's instructions
    - Serious, uncontrolled medical disorder, such as uncontrolled diabetes with documented prior recurrent infections, unstable heart disease or recent cerebrovascular event
    - Known demyelinating disease of the central nervous system or neurological indications thereof
    - Heart failure (NYHA 3 and 4)
    - Cancer within the last 5 years, other than controlled non-metastatic cutaneous squamous cell epithelial/basal cell carcinoma and/or carcinoma in-situ cervix uteri
    - Newly diagnosed SLE or SLE-type disease (positive ANA not a contra-indication)
- Contra-indications for MRI
- Known alcohol/drug abuse
- Inability to give informed consent
- Inability to cooperate with the study programme due to physical or mental reasons

7.3 Exclusion/withdrawal from the study

If the site investigator decides that a participant should be excluded from the study, the primary investigator, co-primary investigator or project leader must be contacted.

- The patient can withdraw from the study at his or her own request at any time.

- The patient can be excluded from the study if the investigator considers this necessary for medical reasons.

If the patient withdraws from the study, the patient will be offered follow-up visits with MRI, X-ray and clinical and biochemical examinations at year 1 and 2.

8 Treatment

At inclusion, all patients will receive DMARD treatment, either in the form of monotherapy or combination therapy with the following DMARDs: Methotrexate (MTX), Sulfasalazine (SSZ), Hydroxychloroquine (HCQ), Leflunomide (LEF).

The treatment may be intensified according to a predefined treatment algorithm (see Section 8.1) at the ordinary 4 months visits, where the disease activity is monitored. Patients exhibiting *unsatisfactory inflammatory activity* (see Section 8.1.2) will move one step up the treatment ladder and receive intra-articular glucocorticoid injection in clinically swollen joints.

8.1 Treatment algorithm

Patients can be included in the study at steps 1, 2 or 2a, depending on medication at the time of inclusion. Biologic treatment is not permitted at the time of inclusion. The patients must not have a known intolerance to MTX treatment, which means that the patient is unable to tolerate as a minimum MTX 7.5 mg (minimum dose).

Step:

1. DMARD monotherapy at less than the maximum tolerated dose*
2. DMARD monotherapy at the maximum tolerated dose**

2a DMARD combination therapy at less that the maximum tolerated doses***

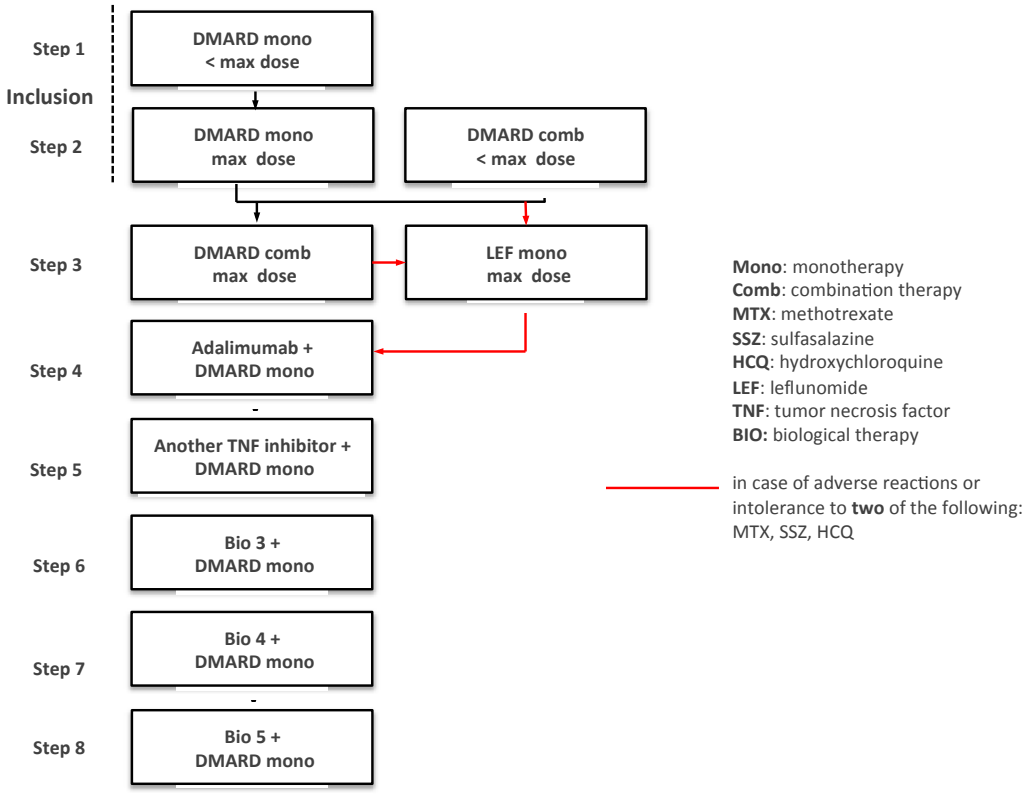
3. DMARD combination therapy at the maximum tolerated doses***

3a LEF*****

4. MTX or LEF or SSZ (prioritised sequence) at the maximum tolerated dose + Adalimumab******
5. MTX or LEF or SSZ (prioritised sequence) at the maximum tolerated dose + other TNF-alpha inhibitor (selected by the attending rheumatologist) ******
6. MTX or LEF or SSZ (prioritised sequence) at the maximum tolerated dose + biological treatment 3 (preferably non-TNF-alpha inhibitor selected by the attending rheumatologist in accordance with the department's instructions) ******
7. MTX or LEF or SSZ (prioritised sequence) at the maximum tolerated dose + biological treatment 4 (preferably non-TNF-alpha inhibitor selected by the attending rheumatologist in accordance with the department's instructions) ******

8. MTX or LEF or SSZ (prioritised sequence) at the maximum tolerated dose + biological treatment 5 (preferably non-TNF-alpha inhibitor selected by the attending rheumatologist in accordance with the department's instructions) ******

*Maximum dose of DMARD monotherapy: up to MTX 25 mg/week, SSZ 3g/day, HCQ 400 mg/day or LEF 20 mg/day
**Maximum dose of DMARD monotherapy: up to MTX 25 mg/week, SSZ 3g/day, HCQ 400 mg/day or LEF 20 mg/day
Minimum dose of DMARD monotherapy: min. MTX 7.5 mg/week, SSZ 1g/day, HCQ 200 mg/day, LEF 10 mg/day
***Maximum dose of DMARD combination therapy: up to MTX 25 mg/week, SSZ 2g/day and HCQ 200 mg/day
****Maximum dose of DMARD combination therapy: up to MTX 25 mg/week, SSZ 3g/day and HCQ 400mg/day
Minimum dose of DMARD combination therapy: min. MTX 7.5 mg/week, SSZ 1g/day, HCQ 200 mg/day
*****In case of adverse reactions or intolerance to two of the following: MTX, SSZ, HCQ in three-drug therapy, change to monotherapy LEF 20mg/day without prior loading dose.
******Biological treatment is administered in combination with DMARD monotherapy treatment in the following prioritised sequence: MTX, LEF, SSZ. If the patient develops adverse reactions to the supplemented DMARD monotherapy treatment and is unable to tolerate the minimum dose, a switch must be made to another DMARD in the above mentioned prioritized sequence.



8.1.1 Treatment at the time of inclusion:

At the time of inclusion the patient can be in DMARD monotherapy treatment (step 1 or 2) OR in combination treatment (2a) in the form of 2- or 3-drug therapy. If the patient is undergoing 3-drug therapy, at least one of the preparations must be administered at less than "maximum inclusion dose".

"Maximum inclusion dose" is defined as MTX 25 mg/week (or maximum tolerated dose if 25 mg/week is not tolerated), SSZ 2g/day (or maximum tolerated dose if 2 g/day is not tolerated) and HCQ 200 mg/day (or maximum tolerated dose if 200 mg/day is not tolerated)

If the patient is not exhibiting *unsatisfactory inflammatory activity* (see Section 8.1.2) this treatment may be maintained throughout the study period. At the time of inclusion, the patient must not have a known intolerance to MTX treatment which means that the patient is unable to tolerate as a minimum MTX 7.5 mg (minimum dose).

8.1.2 Treatment in the case of unsatisfactory inflammatory activity

In the case of unsatisfactory inflammatory activity:

The presence of at least one clinically swollen joint (see Section 11.2.2.) and DAS28>3.2 (Arm A and B) **AND/OR** MRI-detected bone marrow oedema score > 0 with reference to OMERACT RAMRIS score (Arm B), the patient moves one step up the treatment ladder.

Unsatisfactory inflammatory activity at treatment step 1:

Dose increase of DMARD monotherapy within 4 weeks to maximum tolerated dose.
Unsatisfactory inflammatory activity at treatment step 2:
Patients in DMARD monotherapy at the maximum tolerated dose or DMARD combination therapy at less than the maximum tolerated dose, move one step up the treatment ladder to DMARD combination therapy (MTX, SSZ, HCQ) at the maximum tolerated doses (step 3). If not least two of these are tolerated at the minimum dose, treatment with LEF monotherapy is started.
Unsatisfactory inflammatory activity at treatment step 3:
Patients in DMARD combination therapy at the maximum tolerated dose or LEF treatment move one step up the treatment ladder and switch to Adalimumab treatment combined with DMARD monotherapy in the form of either MTX, LEF or SSZ (in prioritised sequence) at the maximum tolerated dose.
Unsatisfactory inflammatory activity at treatment step 4:
Patients in Adalimumab treatment move one step up the treatment ladder and switch to a second TNF inhibitor in accordance with the treating department's instructions. Supplementary treatment with either MTX, LEF or SSZ (in prioritised sequence) at the maximum tolerated dose is continued.
Unsatisfactory inflammatory activity at treatment step 5:
Patients treated with a second TNF-inhibitor switch to a different biological treatment (preferably non-TNF-inhibitor), combined with DMARD monotherapy in the form of either MTX, LEF or SSZ (in prioritised sequence) at the maximum tolerated dose in accordance with the treating department's instructions.
Unsatisfactory inflammatory activity at treatment step 6, 7, 8:
Patients switch biological treatment (preferably to a non-TNF-inhibitor), combined with DMARD monotherapy in the form of either MTX, LEF or SSZ (in prioritised sequence) at the maximum tolerated dose in accordance with the treating department's instructions.

8.1.3 Treatment switch outside ordinary 4-monthly visits:
Generally, a step up the treatment ladder can only occur at the ordinary 4-monthly visits in the case of unsatisfactory inflammatory activity (see Section 8.1.2). Exceptions include:

1) If the patient exhibits *"unacceptably high disease activity"* (DAS28>5.1 and ≥1 clinically swollen joint, where the disease activity cannot be put down to a different disease) and at the ordinary 4-monthly visit:

a) treatment modification has not been carried out, an intra-articular glucocorticoid injection is administered (max. 4 ml) and if unacceptable disease activity persists, the patient can be permitted to move one step up the treatment ladder.

b) treatment modification has been carried out, an intra-articular injection is administered (max. 4 ml) and an extra-ordinary visit is scheduled 2 months later, if the patient is not seen before this at a scheduled ordinary 4-monthly check-up. If unacceptable disease activity persists, the patient can be permitted to move one step up the treatment ladder.

2) If the patient experiences **adverse reactions** to the treatment and the necessary dose reduction or discontinuation causes the patient to experience *unsatisfactory inflammatory*

activity (see Section 8.1.2), intra-articular glucocorticoid (max. 4 ml) is administered and the patient is can move one step up the treatment ladder at an extra-ordinary visit if unsatisfactory disease activity still is present after at least one month. However, a glucocorticoid injection < 6 weeks before the ordinary 4-monthly visit should be avoided if at all possible.

3) If the patient develops **adverse reactions to three-drug therapy (step 3).** In the case of adverse reactions to two of the following: MTX, SSZ, HCQ during three-drug therapy, a switch is made to LEF monotherapy. If adverse reactions occur within 4 weeks of the treatment switch, the next ordinary 4-monthly visit is retained, otherwise the next ordinary visit is moved to 4 months after the start of LEF treatment.

Generally, switching to a different treatment between the ordinary 4-monthly visits means the next ordinary visit will be carried out 4 months after the treatment switch. An exception is made if a treatment modification occurs within 4 weeks of the ordinary 4-monthly visit. In such case, the time of the next ordinary 4-monthly visit is retained.

8.1.4 Methotrexate

MTX is included as part of the three-drug therapy (step 3 on the treatment ladder) and as a preferred DMARD in combination with biological treatment (steps 4-6 on the treatment ladder) at the maximum dose (25 mg/week) or maximum tolerated dose, and with a minimum of one dose of 7.5 mg/week.

Start of peroral MTX: When switching to a combination treatment, if the patient is not in MTX treatment, the starting dose is 15 mg/week, increasing by 5 mg every 2 weeks up to the maximum dose or, if unacceptable adverse reactions occurs, the highest tolerated dose. In the case of gastrointestinal adverse reactions, a switch should be made to a subcutaneous MTX injection before the patient moves one step up the treatment ladder.

Indication for subcutaneous MTX treatment: In the case of adverse reactions in the form of gastrointestinal disorders from peroral MTX treatment <25 mg/week, the patient must be switched to a subcutaneous MTX injection, if there are no contra-indications thereto (e.g. lack of compliance with the injection).

- Start of subcutaneous MTX: The patient is started on subcutaneous MTX once a week with a start dose of 10 mg below the peroral MTX dose which caused the adverse reactions, increasing by 5 mg per week up to the maximum dose (25 mg/week) or, if accompanied by unacceptable adverse reactions, the highest tolerated dose.

8.1.5 Sulfasalazine:

Start SSZ: Start dose of 1g x 1/day for one week, followed by a daily dose increase of 1g at weekly intervals to 1g x 3/day.

Dose escalation SSZ: If the patient is already in SSZ treatment at a dose less than maximum dose, the patient starts immediately treatment with 1g x 3/day.

8.1.6 Leflunomide:

Start LEF: Start dose 20 mg/day. When switching to a different treatment, a wash-out procedure is carried out with 8 g colestyramine x 3/day for 11 days. The patient can switch directly from another DMARD treatment to LEF treatment if his/her liver enzymes appear

normal. Otherwise, the patient must wait 4 weeks or until normalisation of the liver enzymes before starting treatment.

8.1.7 Adalimumab:
Start Adalimumab: 40 mg subcutaneously every 2 weeks.
Administration and handling: Adalimumab will be supplied in the form of a sterile solution without preservatives for subcutaneous injection in a 0.8 ml single-dose pen/syringe containing Adalimumab 40 mg/0.8 ml, for self-injection by the patient every 2 weeks. The medicine is injected subcutaneously in the stomach or thigh. A location a minimum of 3 cm from the previous injection site should be selected for each injection. Injections should not be administered in areas where the skin is sore, where there is redness or bruising, in stretch marks or scars, or where the skin is hard. The first injection will be administered at the rheumatology department, provided that all preliminary tests assessed before biologic treatment are acceptable (assessed by the clinician). At the time of the first injection, all patients will be instructed in the correct subcutaneous injection technique. The second injection is either administered by the patient himself/herself or by a "helper" and/or the injection will be administered at the rheumatology department under the supervision/monitoring of trained staff, if this is deemed necessary. The subsequent injections will be administered outside the departments.

Identification of study drug, storage and usage: see Appendix C

8.1.8 Other biological treatment
If the patient moves one step up the treatment ladder to step 5 or 6, a switch is made respectively to a different TNF-inhibitor (step 5) or another biologic, preferably a non-TNF-inhibitor, in accordance with the department's instructions (step 6).

8.2 Prior and concomitant therapy

8.2.1 Glucocorticoids:
Intra-articular treatment: Intra-articular glucocorticoid treatment must be administered at ordinary 4-monthly visits (in total max. 4 ml) in the case of clinically swollen joints and may be administered in the intervening 4-month period (further maximum of 4 ml glucocorticoids per 4-month period) in the case of *unsatisfactory inflammatory activity* (see Section 8.1.2). However, glucocorticoid administration should as far as possible be avoided < 6 weeks before the scheduled ordinary visit.
Glucocorticoid treatment is preferably administered either as an injection of Diprospan or Lederspan. These preparations will not be supplied and the choice of specific preparation is up to the attending physician based on the department's instructions.
An intra-articular injection of 0.5 – 2.0 ml/joint is administered in all joints with active synovitis, to a maximum of 4 joints and with a maximum of 4 ml of glucocorticoid administered intra-articular per visit. Since a maximum of 4 ml per ordinary 4-monthly visit and a maximum of 4 ml in the intervening 4-month period may be administered, a maximum of approx. 2.6 mg of glucocorticoid can be administered per day over 4 months.

Oral treatment: Oral glucocorticoid administration is NOT permitted. The only exception to this is if the patient has been receiving a stable dose (max. 5.0 mg/day) of the glucocorticoid (prednisolone) for more than 3 months prior to inclusion. In this case the patient must continue with an unchanged dose throughout the study period.

Intramuscular treatment: Intramuscular steroid injection is NOT permitted.

Local, inhalation and nasal application of glucocorticoids is permitted.

8.2.2 Folic acid
All patients in MTX treatment will be treated with at least 5 mg folic acid/week (5 mg x 1-2/week)

8.2.3 Osteoporosis prophylaxis
Calcium and vit-D3: Sufficient calcium (800mg/day) and vitamin D3 (800IE/day) come from food or as a supplement. Otherwise a supplementary tablet of calcium and vitamin D is provided.

Age < 65 years:
Calcium from food < 800 mg/day: Daily supplement of 800 mg calcium + 800 IE vitamin D.
Calcium from food > 800 mg/day: Possible daily supplement of 800 IE vitamin D.
Age > 65 years:
Calcium from food < 800 mg/day: Daily supplement of 1,200 mg calcium + 800 IE vitamin D.
Calcium from food > 800 mg/day: Daily supplement of 800 mg calcium and 800 IE vitamin D (Danish Bone Society's guidelines for assessment and treatment of osteoporosis 2009 (www.dkms.dk)).

Bisphosphonate treatment: Alendronate treatment 70 mg/week is administered to patients with a verified low-energy fracture of the hip and/or back, or with reduced BMD in the hip or back at the time of inclusion, corresponding to a T-score of <-2.5.

8.2.4 NSAID
Treatment with NSAID preparations in stable doses is permitted.

8.2.5 Paracetamol
Treatment with paracetamol (max. 1 g x 4/day) is permitted.

8.2.6 Weak opioids
Treatment with Tramadol and Codein is permitted.

8.2.7 Strong opioids and muscle relaxants
Treatment with strong opioids and muscle relaxants is NOT permitted.

9 Adverse reaction monitoring

At baseline, at each of the ordinary 4-monthly visits and when moving up the treatment ladder, patients will be asked about adverse reactions and laboratory analyses will be carried

out *inter alia* to monitor for adverse reactions (see Section 11.6.1). All unexpected suspected medication-related adverse reactions from inclusion to month 24 are registered in the DANBIO database (see Section 14).

9.1 Methotrexate

Biochemical control analyses (see Section 11.6.1)

9.1.1 Elevated liver enzymes
In case of ALAT increase to > 3 x the upper limit of normal or an unexplained fall in S-albumin > 10%, MTX is paused and extra blood test controls will be performed after 14 days. This procedure is repeated every 14 days until normalisation of liver enzymes (ALAT < 2 x upper value of normal, S-albumin stable or increasing), after which the patient starts MTX at half dose and is stepped up in accordance with the protocol (see Section 8.1.4). In the case of an ALAT increase to > 5 x the upper limit of normal, MTX is discontinued.

9.1.2 Leucopenia, neutropenia, thrombopenia
In case of leucopenia, neutropenia or thrombopenia (with reference to local reference values), MTX is gradually reduced by 2.5 mg/week until normalisation of haematology. Possible folic acid deficiency is corrected in accordance with Danish recommendations. After a further 4 weeks, MTX can again be increased by 2.5 mg/week in accordance with the protocol (see Section 8.1.5).
In case persistent of falling leucopenia (<2.0 10^9/l), neutropenia (<1,2 10^9/l) or thrombopenia <75 10^9/l), treatment is discontinued.

9.1.3 Interstital pneumonitis
In case of progressive lung dysfunction indicating interstitial pneumonitis, an HR-CT scan of the lungs is performed. If the diagnosis is confirmed, MTX is discontinued.

9.2 Hydroxychloroquine

Biochemical control analyses (see Section 11.6.1). After start-up all patients must undergo a check up by an ophthalmologist with regard to retinopathy at the latest 6 months after the start of treatment. Thereafter patients >65 yrs are checked by an ophthalmologist every 6 months (DRS guidelines 2011).

9.3 Leflunomide

Biochemical control analyses (see Section 11.6.1) and BP and weight in accordance with the department's instructions.

9.4 Sulfasalazine and Adalimumab

Biochemical control analyses (see Section 11.6.1) and in accordance with the departments instructions.

9.5 Other biological treatment

When the patient switches from Adalimumab to a different TNF-inhibiting treatment or other biological treatment, biochemical control analyses are also carried out (see Section 11.6.1) and the patient is monitored in accordance with the department's instructions.

10 Endpoints

10.1 Primary clinical endpoint

DAS28 remission (<2.6) at 24 months

10.2 Primary radiographic endpoint

No radiographic progression (assessed by the Sharp/vdHeijde method) from baseline to 24 months.

10.3 Secondary endpoints

DAS28-CRP remission (<2.6) at 12 months:
Remission with reference to ACR/EULAR 2011 criteria at 12 and 24 months
DAS28-CRP at 12 and 24 months
No radiographic progression (Sharp/vdHeijde score) from 0-12 and 12-24 months
Change in Sharp/vdHeijde score from 0-12, 0-24 and 12-24 months
No progression in MRI erosions (RAMRIS) score from 0-12 and 12-24 months
Change in MRI erosion (RAMRIS) score from 0-12, 0-24 and 12-24 months
MRI synovitis (RAMRIS) score at 12 and 24 months
MRI bone marrow oedema (RAMRIS) score at 12 and 24 months
Changes in HAQ from 0-12 and 0-24 months
Changes in SF-36 and EQ-5D from 0-12 and 0-24 months

10.4 Explorative endpoints

Dynamic MRI variable (including initial rate of enhancement (IRE) and maximum enhancement (ME)). At baseline, 4, 8, 12, 16, 20 and 24 months

11 Procedures

11.1 Medical history

At screening visits information is obtained on: gender, age, disease duration, co-morbidity, allergies, previous diseases, complaints from other organ systems (CNS, C-P, G-I, U-G, skin), smoking status, alcohol consumption, medication status. Medical history questions focussing on complaints from other organ systems (CNS, C-P, G-I, U-G, skin) are repeated at month 12 and 24.

11.2 Physical examination

Every effort is made to ensure that the same physician is responsible for performing physical examinations of the patient throughout the study period.

11.2.1 General physical examination
At the inclusion visit, the patient undergoes a full physical examination comprising: inspection of the cavum oris, skin, assessment of lymph node status, heart and lung stethoscopy, examination of the abdomen, and additional focussed examinations, if the patient's medical history suggests another disease may be present.
The examination is performed at screening/inclusion, and at month 12 and 24.
In addition, the patient's height and weight are recorded at the screening visit with regard to ordering an MRI scan.

11.2.2 Joint examination
40 peripheral joints are examined at each visit. The number of swollen and tender joints is registered. The following joints are examined: Right and left shoulder joints, elbow joints, wrists, MCP joints, PIP joints, 1st IP joint, knee joints, ankle joints and MTP joints.

11.3 Vital parameters

Blood pressure and pulse rate are measured at all visits, as well as in accordance with the department's instructions, irrespective of treatment, and at the time of a treatment switch.

11.4 Electrocardiogram

A 12-lead ECG will be performed at screening.

11.5 Pregnancy test

Women capable of bearing children (non-fertile women are defined as post-menopausal for at least 1 year or having undergone surgical sterilisation (bilateral tubal ligation, bilateral oophorectomy or hysterectomy)) must take a pregnancy test (se-HCG) when changing from SSZ monotherapy to a different DMARD treatment or before starting biological treatment, and safe methods of contraception must be used (either: oral contraception, an IUD, a slow-release injection of gestagen, subdermal implantation, hormonal vaginal ring or transdermal slow-release patch) throughout the study period.
Se-HCG will be analysed at the department where the test is performed.

11.6 Biochemistry

11.6.1 Conventional biochemical analyses blood tests (control blood tests):
Blood tests (control blood tests) are carried out at screening, before the 4-monthly visits and at the time of a treatment switch, in the form of: haemoglobin, leucocytes and differential count, CRP, thrombocytes, albumin, creatinine, electrolytes, alkaline phosphatases, ALAT.

An examination for anti-CCP and IgM-RF is also performed at screening, and subsequently repeated at month 12 and 24, as well as an examination for ANA and anti-ds-DNA, which is repeated if there is clinical suspicion of medication-induced SLE during biological treatment.

Urine analysis
Urine analysis is carried out at the time of inclusion, as well as before the start of biological treatment and in accordance with the department's instructions, to assess albumin, blood, glucose, leucocytes and nitrite.
The tests are analysed at the biochemical department at which they are performed.

11.6.2 Experimental blood and urine samples
The patient will be asked to give blood for project blood and urine samples every 4 months at the same time as the scheduled blood tests take place, ie. upon inclusion and after 4, 8, 12, 16, 20, and 24 months. The patient will have to give 60 ml of blood for the project samples per visit (whole blood for Pax-gene RNA tubes, blood to serum, EDTA plasma, citrate plasma and heparin plasma). In addition, 20 ml whole blood in EDTA glass will be taken at the inclusion visit. The amount of urine delivered is 10 ml per sample.

The following biomarkers will be determined: 1) VEGF, YKL-40, IL-6 and other interleukins (biomarkers for inflammation); 2) CTX-II, total aggrecan, COMP, MMP-3, helix2, and TIMP-1 (biomarkers for cartilage metabolism); 3) Osteocalcin, CTX-I, pyridinoline, OPG and RANK-L (bone turnover biomarkers); 4) Metabolites; 5) Single nucleotide polymorphisms (SNPs); 6) Gene Expressions; and 7) MicroRNA Expressions. In addition, blood and urine will be stored in a biobank for later analysis of relevant biomarkers.

11.7 Procedures prior to start of biological treatment

In addition to the abovementioned procedures, prior to the start of biological treatment the following will be carried out:

- Supplementary medical history assessment with reference to contra-indications for TNF-inhibiting treatment
- X-ray examination of the thorax if > 6 months old
- Anti-HCV, Hbs-Ag and possible HIV (if none available < 2 years)
- Quantiferon test
- Urine ABS, leucocytes and nitrite
- Serum HCG (fertile women) (see Section 11.5).

11.7.1 Supplementary medical history assessment
Questions which the patient has previously been asked at the inclusion visit concerning current and previous diseases, focussing on the following conditions which could contra-indicate the start of biological treatment, are repeated and involve the following:

- Active infections or chronic infections requiring treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days of the start of TNF-inhibiting treatment

- Immunosuppressive status or HIV infection
- Active or chronic hepatitis B and/or C virus infection
- Persons with latent TB (positive Quantiferon test or thorax X-ray examination indicating TB) or other risk factors for activation of latent TB in patients who have not undergone treatment for latent TB in accordance with the treating department's instructions
- Serious, uncontrolled medical disorder, such as uncontrolled diabetes with documented prior recurrent infections, unstable heart disease or recent cerebrovascular event
- Known demyelinating disease of the central nervous system or neurological indications thereof
- Heart failure (NYHA 3 and 4)
- Malign disease within the last 5 years, other than controlled non-metastatic cutaneous squamous cell epithelial/basal cell carcinoma and/or carcinoma in-situ cervix uteri
- Newly diagnosed SLE or SLE-type disease

11.7.2 X-ray examination of the thorax

An X-ray examination of the thorax is performed with regard to screening for tuberculosis (TB). If an X-ray of the thorax is already available, this must not be more than 6 months old. If the X-ray of the thorax indicates latent TB, the patient must undergo treatment for latent TB in accordance with the department's instructions.

11.7.3 Quantiferon test

A Quantiferon test is performed prior to the start of biological treatment, in accordance with the treating department's guidelines. If the patient has latent TB, which is indicated by a positive quantiferon test or other risk factors for activation of latent TB, the patient must undergo treatment for latent TB in accordance with the department's instructions.

11.7.4 Hepatitis

After obtaining informed consent, the patient is screened for hepatitis B and C (HBsAg, anti-HBs, anti-HCV).

11.8 Assessment of disease activity and general condition

At each visit, the patient fills out an HAQ form to measure disease activity, function level, pain and the rheumatism's overall impact on everyday life.

11.8.1 Health Assessment Questionnaire HAQ (see Appendix D)

The patient's function level is assessed based on the function level index calculation from the HAQ form. The 20 questions in the questionnaire assess the patient's ability to perform tasks in 8 function areas (dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities). The degree of difficulty in each category is assessed from 0 to 3, where 0 represents no difficulty and 3 indicates inability to perform the task. The HAQ Disability Index (HAQ-DI) is calculated as an average of the highest score in each of the 8 categories.

11.8.2 The patient's assessment of his/her own state of health (SF36, EQ-5D)

Questionnaires concerning health-related quality of life (EQ-5D) and self-assessed health (SF-36) are completed at the inclusion visit and at visits in months 12 and 24. (see Appendix E).

11.8.3 The patient's assessment of his/her own pain (patient VAS pain)
The patient indicates pain intensity on visual analogue scale (VAS). The scale is a line 100 mm long with "anchor words" at each end: "no pain" at 0 and "worst imaginable pain" at 100 mm. The patient places a mark (a vertical line) on the line and the distance (in mm) from "no pain" to the patent's mark is measured.

11.8.4 The patient's and the doctor's overall assessment of the impact of the disease on everyday life (patient VAS global and doctor VAS global)
The patient and doctor make an individual assessment, independent of one another, of the overall disease activity on a 100 mm VAS with the "anchor words" "very good" to "very bad".

11.8.5 The patient's own assessment of fatigue (patient VAS fatigue**)**
The patient indicates the extent of fatigue on a 100 mm VAS with the "anchor words" "no fatigue" to "worst imaginable fatigue".

11.8.6 Duration of morning stiffness
The duration in minutes of morning stiffness the day before the visit is noted.

11.9 Imaging diagnostics

11.9.1 Conventional X-ray examination
Conventional X-ray of the hands, wrists and feet.
Time of X-ray:
X-ray will be performed at the time of inclusion and at month 12 and 24.
The X-ray images of the hands and wrists are obtained with a posterior/anterior projection and of the feet with an anterior/posterior projection.

11.9.2 MRI
MRI of the unilateral 2nd to 5th MCP and wrist of the dominant hand.
STIR (Short Tau Inversion Recovery) sequence is recorded prior to contrast agent administration. T1-weighted MRI images are obtained before and after i.v administration of the contrast medium, and if technically possible, dynamic MRI sequences are obtained in connection with contrast administration. In addition for patients scanned at Herlev hospital a diffusion weighted image sequence is obtained.

Time of MRI:
MRI will be carried out on all patients at the time of inclusion and at month 12 and 24. Participants in Arm B will also undergo MRI every 4 months, prior to the ordinary 4-monthly visit. MRI of patients in Arm B must be carried out between 10 and 18 days prior to inclusion and ordinary 4-monthly visits.
Contrast medium: An i.v. injection of 0.1mmol Dotarem (Gadoteric Acid (Dotarem), Guerbet, Paris) per kg body weight is used in connection with MRI.
Duration of MR scan: MR scan time is approx. 40 mins.

11.9.3 Evaluation of imaging

After study termination X-rays of the hands, wrists and feet, as well as MRI scans will be assessed separately by 2 evaluators trained and experienced in evaluation using the Sharp/vdHeijde and RAMRIS scoring methods respectively.

Primary evaluation:
MRI images (Arm B) carried out prior to ordinary 4-monthly visits are immediately transferred electronically (if possible) or send on a CD-ROM from the participating departments to a central centre (Slagelse Hospital). Immediately after this, an experienced evaluator (BE) will evaluate the images to determine the presence/absence of bone marrow oedema and information relating to this will be sent to the respective departments, so that a response is received within one week of the images being sent to the evaluator. The evaluator will be blinded to chronology, clinical, biochemical and other image data.

Evaluation after study termination:
X-ray images and MR scans will be anonymised and the assessor will be blinded to clinical, biochemical and other image data, but not to chronology.

- X-ray of hands, wrists and feet:
  Bone erosions and joint-space narrowing are assessed using the Sharp/vdHeijde scoring method [26, 38]

- MRI of unilateral 2nd to 5th MCP and wrist on dominant side:
  Bone erosions, synovitis and bone marrow oedema are assessed separately using the semi-quantitative scoring system, RAMRIS (RA MRI scoring system) developed through the OMERACT (Outcome Measures in Rheumatology) initiative[33].

11.9.4 Quality assurance
The participating radiology departments also send a CD-ROM containing all MR scans and X-ray images to the Department of Radiology at Herlev Hospital for archiving and quality assurance. The technical quality of the MRI images will be checked by an experience radiographer (JM) and an evaluator (BE). The evaluator (BE) checks the quality of the MRI images taken at the 4-monthly control visits (Arm B) at the same time as the bone marrow oedema evaluation. The radiographer (JM) will check the quality of the MRI images (Arm A) and X-ray images taken at baseline and at month 12 and 24. Quality assurance of MRI images involves checking that the recording covers the correct region, that the stipulated sequence parameters have been used and that the image quality of the sequences is acceptable, including that the images are not contaminated by technical or physiological artefacts. Quality assurance of X-ray images checks that the correct projections have been obtained and that the image quality is acceptable.

If the MRI images do not satisfy the quality requirements, a re-scan and/or repeat X-ray examination of the patient will be carried out. The result of the re-scan must be available no later than 4 weeks after the original scan. Patients must receive the result at the latest 4 weeks after the originally scheduled 4-monthly visit so that subsequent scheduled 4-monthly visits can be maintained if a change in treatment is implemented. If a re-scan cannot be carried out within the accepted maximum 4-week period, the original scan is used as the basis

for treatment (Arm B), if possible, and the scan is deferred to the next scheduled 4-monthly visit.

11.10 Evaluation of disease activity

11.10.1 Disease Activity Score for 28 joints (DAS28)
DAS28 is calculated on the basis of CRP (DAS28-CRP). The composite index is calculated at each visit (see Appendix F).

11.10.2 The 2011 ACR/EULAR definition of remission in rheumatoid arthritis clinical trials
see Appendix G

12 Visits

Procedures and examinations assessed at study visits are described below. Reference is also made to the visit flow-chart (see Section 12.5)

12.1 Screening

The patient receives information on the study orally and in writing. Informed consent and the patient's signature on the consent declaration must be obtained before screening can begin. Information is obtained and registered in relation to: gender, age, height, weight, number of years since symptom onset and year of RA diagnosis, allergies, co-morbidity, previous diseases, registration of medication status (including information on current and prior anti-rheumatic treatment), complaints from other organ systems (CNS, C-P, G-I, U-G, skin), smoking status, alcohol consumption.

The following procedures are carried out and the following data registered:

- Oral and written information on the study
- Declaration of informed consent is signed
- Patient power of attorney is signed
- Inclusion and exclusion criteria are reviewed (see Section 7.1 and 7.2)
- Registration of fulfilment of ACR/EULAR 2010 and ACR 1987 classification criteria respectively.
- Registration of medication status (including information on current and prior anti-rheumatic treatment)
- General physical examination (see Section 11.2)
- 40-joint examination (EULAR)
- BP and pulse rate
- Control blood tests
- IgM-RF
- anti-CCP
- ANA and Anti-ds-DNA
- Urine ABS, including nitrite and leucocytes
- HAQ form

- ECG
- Patient VAS global
- Doctor VAS global
- Patient VAS pain
- Patient VAS fatigue
- Registration of duration of morning stiffness
- DAS28 (CRP) score
- Ordering of MRI of 2nd to 5th MCP and wrist, dominant side*
- Ordering of X-ray of the hands, wrists and feet
- Screening number

*MRI scan is performed between 10 and 18 days prior to the inclusion visit.

The patient can be included if he/she fulfils all the inclusion criteria and none of the exclusion criteria.

12.1.1: Screening number
All screened patients are in each department are assigned a consecutive computer generated number (e.g. S1, S2).

12.2 Procedures common to all ordinary 4-monthly visits (from inclusion to month 24)

- 40-joint examination (EULAR)
- Pulse rate and BP
- Control blood tests (results available at visits)
- Experimental blood and urine sample for biobank storage
- HAQ form
- Doctor VAS global
- Patient VAS global
- Patient VAS pain
- Patient VAS fatigue
- Registration of duration of morning stiffness
- DAS28 (CRP) score
- MRI of 2nd to 5th MCP and wrist on dominant side (Arm B)
- Joint injection with glucocorticoid in the case of clinically swollen joints
- Registration of adverse reactions
- DANBIO registration

12.2.1 Extra procedures related to inclusion visits
In addition to the abovementioned common procedures (see Section 12.2), the following procedures will be carried out where appropriate at the time of inclusion:

- Inclusion and exclusion criteria are reviewed again
- X-ray of hands and feet
- MRI of 2nd to 5th MCP and wrist of the dominant hand (Arm A)
- SF-36

- EQ-5D
- The patient is assigned an inclusion number (e.g. R123)
- Randomisation

Inclusion number:
All patients included are assigned a consecutive computer generated number (e.g. R1, R2). The screening number and inclusion number cannot therefore be mixed up.

12.2.2 Extra procedures in relation to month 12 and 24

- General physical examination (see Section 11.2)
- Anti-CCP
- IgM-RF
- X-ray of hands, wrists and feet
- MRI of 2nd to 5th MCP and wrist of the dominant hand (Arm A)
- SF-36
- EQ5D

12.2.3 Extra procedures in relation to the start of biological treatment

- Contra-indications for TNF-alpha-inhibiting treatment are reviewed:
    - Active infections or chronic infections requiring treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days of the start of TNF-inhibiting treatment
    - Immunosuppressive status or HIV infection
    - Active or chronic hepatitis B and/or C virus infection
    - Persons with latent TB (positive Quantiferon test or thorax X-ray examination indicating TB) or other risk factors for activation of latent TB in patients who have not undergone treatment for latent TB in accordance with the treating department's instructions
    - Serious, uncontrolled medical disorder, such as uncontrolled diabetes with documented prior recurrent infections, unstable heart disease or recent cerebrovascular event
    - Known demyelinating disease of the central nervous system or neurological indications thereof
    - Heart failure (NYHA 3 and 4)
    - Malignant disease within the last 5 years, other than controlled non-metastatic cutaneous squamous cell epithelial/basal cell carcinoma and/or carcinoma in-situ cervix uteri
    - Newly diagnosed SLE or SLE-type disease
    - Current pregnancy or wish to become pregnant
- X-ray of thorax (if > 6 months)
- HBsAg, anti-HBs, anti-HCV and HIV if > 2 years
- Quantiferon test
- Urine ABS, including nitrite and leucocytes

- Serum HCG (fertile women)

12.2.4 Medication-related adverse reactions
At all visits from the inclusion visit up to and including month 24, all suspected serious medication-related adverse reactions are recorded in the DANBIO database, including the CRF (see Section 14).

12.3 Procedures for extra-ordinary visits

The following procedures must be carried out at each extra-ordinary visit:
- 40-joint examination (EULAR)
- Pulse rate and BP
- Control blood tests
- Experimental blood and urine sample for biobank storage*
- Urine ABS, including nitrite and leucocytes (where appropriate)
- HAQ form
- Doctor VAS global
- Patient VAS global
- Patient VAS pain
- Patient VAS fatigue
- DAS28 (CRP) score
- Possible intra-articular glucocorticoid injection in case of clinically swollen joints**
- Registration of adverse reactions
- DANBIO registration

* Collected only in case of treatment intensification.
**If at all possible, intra-articular glucocorticoid < 6 weeks before the next ordinary visit should be avoided.

12.3.1 Procedures in case of a flare-up of disease activity
If the patient attends an extra-ordinary visit and exhibits *unsatisfactory inflammatory activity* (see Section 8.1.2), the abovementioned procedures are carried out and the patient will then be subject to the procedures mentioned in Section 12.2 and maintain the schedule for the ordinary 4-monthly visit (if no change in treatment is implemented).

12.3.2 Procedures in case of a treatment switch outside ordinary 4-monthly visits
If the patient moves a step up the treatment ladder outside ordinary 4-monthly visits (see Section 8.1.3), the patient's next ordinary visit entailing the relevant procedures will be carried out 4 months after the patient's move up the treatment ladder. The patient will undergo procedures mentioned in Section 12.2 at an interval of 4 months.

12.4 Procedures in case of exclusion/withdrawal from the study

The following procedures are carried out if the patient is excluded/withdrawn from the study:
- General physical examination
- 40-joint examination (EULAR)
- Pulse rate and BP

- Control blood tests
- Experimental blood and urine sample for biobank storage
- Anti-CCP
- IgM-RF
- HAQ form
- Doctor VAS global
- Patient VAS global
- Patient VAS pain
- Patient VAS fatigue
- Registration of duration of morning stiffness
- DAS28 (CRP) score
- X-ray of hands, wrists and feet
- MRI of 2nd to 5th MCP and wrist of the dominant hand
- Joint injection with glucocorticoid in the case of clinically swollen joints
- Registration of adverse reactions
- DANBIO registration

The above mentioned procedures are carried out at month 12 and 24

12.5 IMAGINE flow-chart

Visit no	Scre-ening 0	Inclu-sion 1	2	3	4	5	6	7	Extra visit.	Ex-clusion[a]
Visit month	- 4-0[b]- weeks	0	4	8	12	16	20	24	?	?
Control margin (+/- days)[c]	7	0	14	14	14	14	14	14		
Study-related procedures:										
Informed consent	X									
Patient power of attorney	X									
Inclusion and exclusion criteria.	X	X								
Registration of ACR/EULAR 2010 and ACR 1987 criteria	X									
Screening number	X									
Inclusion number		X								
Medical history										
Demographics	X									
Medical history	X				X			X	(X)	
Physical examination										
Physical examination (see 11.2.1)	X	X			X			X	(X)	X
40-joint examination	X	X	X	X	X	X	X	X	X	X
Pulse rate and BP	X	X	X	X	X	X	X	X	X	X
Height and weight	X									
ECG	X									
Biochemical examinations										
Control blood tests (see 11.6.1)[d]	X	X	X	X	X	X	X	X	X	X
Experimental blood and urine sapmples		X	X	X	X	X	X	X	X[h]	X
Anti-CCP	X				X			X		X
IgM-RF	X				X			X		X
ANA and Anti-ds-DNA[e]	X			(X)	(X)	(X)	(X)	(X)	(X)	(X)
Urine ABS, leucocytes and nitrite[f]	X			(X)	(X)	(X)	(X)	(X)	(X)	(X)
Serum HCG (see 11.5)		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Disease activity and function level										
HAQ	X	X	X	X	X	X	X	X	X	X
Pt. VAS pain	X	X	X	X	X	X	X	X	X	X
Pt. VAS global	X	X	X	X	X	X	X	X	X	X
Doctor VAS global	X	X	X	X	X	X	X	X	X	X
Pt. VAS fatigue	X	X	X	X	X	X	X	X	X	X
Morning stiffness (min)	X	X	X	X	X	X	X	X	X	X
DAS28 (CRP) score	X	X	X	X	X	X	X	X	X	X
SF-36 and EQ-5D		X			X			X		
Image diagnostics										
X-ray of hands and feet		X			X			X		X
MRI of 2nd to 5th MCP and wrist (Arm A)		X			X			X		X
MRI of 2nd to 5th MCP and wrist (Arm B)[g]		X	X	X	X	X	X	X		X
Other procedures										
Joint injection in case of joint inflammation (see 8.2.1)		X	X	X	X	X	X	X	(X)	X
DANBIO registration		X	X	X	X	X	X	X	X	X
Registration of adverse reactions		X	X	X	X	X	X	X	X	X

[a] Procedures carried out month 12 and 24
[b] Inclusion is performed within 4 weeks after screening and no earlier than 10-18 days after MR scan is performed. The exception is, however, if it can not be documented that the patient has had low disease activity/remission (DAS <3.2) at least 4 weeks prior to inclusion. In this case, inclusion must be made minimum 4 and maximum 6 weeks after screening.
[c] Visits can be moved with +/- 14 days calculated from the date of visit 1
[d] haemoglobin, leucocytes and differential count, CRP, thrombocytes, albumin, creatinine, electrolytes, alkaline phosphatases, ALAT
[e] Examined during screening and subsequently if there is clinical suspicion of medication-induced SLE during biological treatment
[f] Examined during screening, before the start of biological treatment and where appropriate
[g] MRIs must be performed 10-18 days prior to visits
[h] Only in case of treatment intensification

13 Statistics

13.1 Statistical power and sample size calculation

13.1.1 Primary clinical endpoint

Assuming 60% of patients treated by conventional clinical/biochemical examination and 80% of the patients treated by conventional clinical/biochemical examination and MRI findings reach the primary clinical endpoint (DAS<2.6) at month 24, a group size of 64 in each group is assumed to give a statistical power of 80% (beta=0.20) for the detection of statistically 1-sided significant (p=0.05) treatment efficacy, assessed on the basis of two independent binomially distributed proportions using Pearson's chi-square statistics with a chi-square approximation with a 1-sided significance level of 0.05. Based on the specified group size of 100 patients in each group (200 in total), the project is assessed as having a 93% chance of success with regard to the clinical endpoint (statistical power 0.93).

13.2.1 Primary radiographic endpoint

Primary radiographic endpoint (assessed using the Sharp/vdHeijde score):
Assuming that 75% of the patients treated by conventional clinical/biochemical examination[1] and 90% of the patients treated by conventional clinical/biochemical examination and MRI findings reach the primary radiographic endpoint (no radiographic progression) at month 24, a group size of 79 in each group will be assumed to give a power of 80% (beta=0.20) for detection of a statistically 1-sided significant (p=0.05) treatment efficacy, assessed on the basis of two independent binomially distributed proportions using Pearson's chi-square statistics with a chi-square approximation with a 1-sided significance level of 0.05. Based on the specified group size of 100 patients in each group (200 in total), the project is assessed as having an 88% chance of success with regard to the radiographic efficacy goal (statistical power 0.879).

Based on "sample size" calculations of the two abovementioned endpoints, a total "sample size" of 200 has been determined.

13.2 Overall statistical analysis

The proportion of patients in the 2 treatment groups who fulfil the primary endpoint (and secondary endpoints) will be compared using the chi-square test. The primary analysis will be based on the total ITT (Intention-to-treat) population; all patients randomised. The primary statistical analysis will be based on all usable data, irrespective of protocol deviations, and missing data will primarily be replaced using 'multiple imputation' which assumes that data is 'Missing At Random' (Sterne JA, BMJ 2009); these analyses will secondarily be supplemented

by 'Worst-Case' and 'Best-Case' imputation in the event that data is 'Not Missing At Random' (White IR, BMJ 2011).
With regard to the further hypothesis-generating component of the project, a separate analysis of the patients who adhered to the protocol (per-protocol analysis) will be carried out.

[1] *The AMBRA study which is ongoing at King Christian X´s Hospital at Gråsten and Vejle Hospital and involves 300 patients with RA in accordance with the ACR 1987 classification criteria, DAS28<3.2, ≥ 1½ year's disease duration, unchanged anti-rheumatic treatment ≥ 3 months and no biological treatment. The patients are monitored in different outpatient clinics, treated with DMARDs and if necessary biological treatment to maintain a low disease activity based on clinical evaluation. Radiographic progression in wrists, hands and feet 0 – 24 months was seen in 25% of patients who were anti-CCP positive and had erosive disease at the time of inclusion. The proportion of patients with DAS28>2.6 was 38%.*

13.2.1 Estimated proportion of patients at the various stages of the treatment algorithm in the study
If, at the time of inclusion, the patients are divided as in the AMBRA study (see [1], above) 30% of the patients in steps 1 to 3 will move one step up the treatment ladder every 4 months, and the proportion of patients at the various stages at the various times will be as follows:

Steps	Baseline	4 months	8 months	12 months	16 months	20 months
1. Mono<max	60%	42%	29%	21%	14%	10%
2. Mono max	20%	32%	35%	33%	30%	25%
3. Comb<max	20%	20%	24%	26%	28%	28%
4. Comb max	-	6%	10%	15%	17%	17%
5. Bio 1 (Ada)	-	-	2%	4%	9%	14%
6. Bio 2	-	-	-	1%	2%	5%
7. Bio 3	-	-	-	-	-	1%

According to this estimation model, the total time on bio1 (Adalimumab) over the entire study period will be 18.2 years (total number of doses with 200 patients will be 934 doses if 27 doses/year), whereas the total time on bio 2 will be 8.0 years and on bio 3, 0.6 years.
The total number of years on biological preparations other than Adalimumab is therefore estimated at 8.6 years.

14 Adverse reactions/adverse events

It is the responsibility of the investigator to ensure that all adverse reactions/adverse events are reported and registered on the proper forms. It is also the investigator's responsibility to ensure that all serious adverse reactions/adverse events are immediately reported to Kim Hørslev-Petersen (sponsor), Mikkel Østergaard (co-sponsor) or the project leader Signe

Møller-Bisgaard who are responsible for notifying the regional Biomedical Research Ethics Committee. Reports to the regional Biomedical Research Ethics Committee must be accompanied by comments on the possible consequences for the trial. The project leader is also responsible for informing the participating departments of what a serious adverse reaction/adverse event entails. It is also the responsibility of the project leader to submit on an annual basis, starting one year after approval of the study, a list of all serious unexpected adverse reactions and serious adverse events (see Section 14.1) that have occurred in the period, to the regional Biomedical Research Ethics Committee. Reports must be accompanied by an assessment of the safety of trial subjects. Where possible, the diagnosis must be registered. If a diagnosis cannot be determined, the individual indications and symptoms must be registered as individual adverse events/adverse reactions.

14.1 Definition of adverse reactions/adverse events

(Danish Medicines Agency guideline concerning regulations for clinical trials)

- Adverse event: any adverse event in a patient or subject in a clinical trial after treatment with a medicine, whether or not there is a causal relationship between this treatment and the adverse event.

- Adverse reaction: any harmful and adverse reaction to an investigational medicinal product, irrespective of dose

- Unexpected adverse reaction: an adverse reaction which in nature or extent does not accord with product information provided (e.g. the investigator's brochure for a non-approved investigational medicinal product or the summary of product characteristics in the case of an approved product)

- Serious adverse event or serious adverse reaction: an adverse event or adverse reaction which, irrespective of dose, results in death, is life-threatening, necessitates hospital admission or an extension of hospitalisation, results in significant or permanent invalidity or professional incapacity, or causes a congenital anomaly or malformation.

14.1.1 Unexpected adverse events include the following:

- Any suspected adverse reactions.
- Any reaction connected with the medicine resulting from overdosing, misuse, discontinuation, hypersensitivity or toxicity.
- Apparently unrelated diseases, including exacerbation of existing diseases.
- Injury or accident
- Abnormal results from physiological analysis or findings from physical examinations requiring clinical intervention or further examination
- Abnormal laboratory results requiring clinical intervention or further examination, unless these are connected with a clinical adverse event which has already been reported.

14.1.2 Existing conditions

In this study, an existing condition (i.e. a disorder which was present prior to the beginning of the period for reporting unexpected adverse events and registered in medical records/by physical examination prior to treatment) should not be reported as an unexpected adverse event unless the condition is exacerbated or the frequency of episodes increases in the course of the "period for reporting unexpected adverse events" (see Section 14.2.1).

14.1.3 Disease exacerbation
Disease exacerbation should not be reported as an unexpected adverse event unless these indicators or symptoms satisfy one or more the specified serious criteria (14.1), or the patient withdraws from the trial due to these indicators or symptoms.

14.1.4 Procedures
Invasive and non-invasive diagnostic and therapeutic procedures, e.g. operations, are not reported as unexpected adverse events. A medical condition for which an unscheduled procedure has been performed should however be reported if it satisfies the definition of a serious unexpected adverse event (see Section 14.1). For example, acute appendicitis must be reported as an unexpected adverse event, but not the appendectomy itself.

14.2 Reporting procedures for unexpected adverse events

14.2.1 Period for reporting unexpected adverse events
The period for reporting unexpected adverse events in this trial begins at the screening visit and ends at the final study visit.

14.2.2 Registering unexpected adverse events
The investigator must register all directly observed unexpected adverse events and all unexpected adverse events reported unsolicitedly by the patient. In addition every individual patient must be questioned about unexpected adverse events at every clinical visit. General questions are asked, such as “have you had any health problems?" or "have you had any health problems since your last visit to the clinic?". It is the responsibility of the investigator to ensure that all unexpected adverse events, including all serious unexpected adverse events/adverse reactions, are registered in the section for registering unexpected adverse events in DANBIO and in the appropriate document in the CRF. It is also the investigator’s responsibility to ensure that all serious unexpected adverse events, irrespective of whether they are caused by the trial medicine, are reported to the sponsor Kim Hørslev-Petersen, the co-primary investigator Mikkel Østergaard or the project leader Signe Møller-Bisgaard at the latest 24 hours after the occurrence of the adverse event becomes known.

14.2.3 Unexpected adverse events in connection with Adalimumab treatment
Unexpected adverse events are reported as specified in Section 14.2. In addition, it is the responsibility of the sponsor to report all serious adverse events linked to Adalimumab to AbbVie Laboratories A/S at the latest 24 hours after the occurrence of the adverse event becomes known.

15 Quality assurance and quality control

15.1 Good Clinical Practice (GCP) regulations

The study is being carried out in cooperation with the GCP unit in Copenhagen. A GCP monitoring programme will be developed with internal monitoring of the study.

15.1.1 Initiation meeting

Before the inclusion of patients, each individual study centre will hold an initiation meeting at which either the primary investigator or co-primary investigator and/or the project leader and staff from the participating department will be present. This meeting will involve a detailed discussion of the protocol and cover the implementation of trial procedures and completion of the CRF.

15.1.2 Study monitoring

A GCP monitoring plan will be developed in cooperation with the GCP unit in Copenhagen to ensure that the trial is carried out, registered and reported in accordance with the protocol, with specified procedures and with Danish law. Monitoring will be carried out by internal monitors who will be responsible for the monitoring.

15.1.3 Case Report Forms (CRFs)

An electronic CRF is filled out for each enrolled patient. As in general everyday clinical practice, the patient's data will be registered electronically in the DANBIO database. All study-related data will be registered in study-specific electronic CRFs drawn up in DANBIO. Only personnel involved in the study will have access to these. The CRFs will be completed by the investigator, the project nurse and the patient and will contain information from the patient's medical records, patient interviews and the patient's reported questionnaires. Data is then exported to a special Opera-version of DANBIO, which only the monitor has access to. The monitor's data corrections/additions are saved at field level so it is obvious what the Monitor has changed.
Analyses carried out at a later time on the basis of the data, will be based on data from the special Opera-version of DANBIO, i.e. once the data is copied from danbio-online.dk to the special Opera-version, only the Monitor can then, on the basis of queries, correct/make additions to the data used in the project's analyses. General data management and validation are performed by Niels Steen Krogh, Zitelab aps, Copenhagen.
Test results not available electronically will be stored in the patient's medical records.

15.1.6 Biochemical analyses

Routine haematological analyses are carried out locally and the results are entered in the CRF where relevant.

15.1.7 Storage of personal information/Danish Data Protection Agency

To give the health authorities the option of further evaluation, the investigator registers, *inter alia*, the identities of all participating patients (enough information to link the registrations, e.g. CRFs and hospital journals) and stores all original signed informed consent forms and electronic CRFs. In accordance with international regulations, the investigator must store these registrations for a minimum of 10 years.

Patient data is protected in accordance with the Danish Act on the Processing of Personal Data and the Danish Health Act. The Danish Data Protection Agency will be notified about the project.

15.1.8 Access to data sources/documents

The original completed CRFs belong to the investigator and may not be made available in any form to third parties, other than authorised representatives of the relevant health and supervisory authorities and the trial monitor.
The investigator is permitted direct access to source documents/data, including medical records during monitoring, auditing and/or inspection by the research ethics committee.

16 Ethical considerations

The trial will be carried out in accordance with recommendations concerning biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, with subsequent revisions.
Good Clinical Practice (GCP) requires that the clinical protocol, all protocol amendments, the declaration of informed consent and all other forms of participant information (e.g. advertisements for the recruitment of participants) and all other necessary documents must be assessed by the Biomedical Research Ethics Committee. Approval of the protocol, the declaration of informed consent, all information for participation and/or any advertisements will be obtained from the Biomedical Research Ethics Committee prior to the beginning of the trial. Any protocol amendment requires approval from the Biomedical Research Ethics Committee prior to implementation of the amendments in the trial design.
In the course of the trial the investigator must immediately submit written reports to the Biomedical Research Ethics Committee concerning any amendment which affects implementation of the trial and/or increases the risk to participants.

16.1 Ethical considerations concerning this study

Patients included in this study are RA patients with erosive disease in low disease activity/remission. In this study, the patients will receive DMARD standard treatment (monotherapy or combination therapy), which is also applied in everyday clinical practice. Treatment with intra-articular glucocorticoid injection in case of disease flare-up and possible treatment with paracetamol and weak opioids is permitted to ensure the patient receives optimal treatment between visits and is consistent with everyday clinical practice. In this study, the patient may receive intensified DMARD treatment more quickly than is conventionally the case and start biological treatment if MRI changes in the form of bone marrow oedema are present. This must be considered permissible as it is expected that intensification based on MRI findings can stop/prevent further erosive progression with serious damage to the joint's cartilage and bones and resultant function loss. The anticipated preventive benefits from intensification of DMARD treatment and biological treatment, initially in the form of TNF-inhibiting treatment, clearly outweigh the acknowledged risks of adverse reactions.

MRI of the hand and wrist is not linked to any known adverse reactions or problems apart from discomfort from lying still and pain/discomfort from the placement of intravenous

access in the bend in the elbow for intravenous contrast agent administration. There are not thought to be any harmful effects on humans from exposure to very powerful magnetic fields up to 8 tesla, and probably higher. Although MRI using powerful 3-tesla magnetic fields has only been used in recent years, more powerful field types and field changes have been used since the 1950s, e.g. in connection with radar, accelerators and research.
For optimal visualisation of the structures involved in joint inflammation during MRI, venous administration of a small quantity of a non-radioactive contrast medium is required. In rare cases administration can be linked to a temporary sensation of heat and pain at the injection site. The risk of a critical allergic reaction to the specific MR contrast agent is considered less than 1:100,000, and the MR department is prepared to instigate the relevant treatment should this become necessary. Another rare but well-known adverse reaction to certain MR contrast agents is nephrogenic systemic fibrosis. This however is only seen in patients with severe renal disorders who are exposed to MR contrast agents. This adverse reaction has not been observed in patients with normal renal function. Project participants are examined and blood samples taken before MRI to exclude renal disorders. The contrast medium used, Dotarem, has been assessed by the EMEA as being a low-risk contrast agent and globally more than 200 million patients have undergone MR scans using Dotarem.
X-ray examination of hands, wrists and feet expose patients to a radiation dose corresponding to, or less than, 0.002 mSv. This risk is considered to be insignificant (Appendix 5 "Guidelines on the use of ionising radiation in a biomedical research trial", Danish National Committee on Biomedical Research Ethics) and the frequency is consistent with everyday clinical practice. Urine testing, and the frequency of, and quantity of blood taken for, blood tests to determine adverse reaction variables, as well as the screening programme prior to the start of biological treatment, are consistent with everyday clinical practice.
This study is expected to contribute significant new knowledge about the options for enhanced treatment of RA patients in the form of better and more sensitive disease monitoring and thereby optimise clinical and radiographic disease control. The potential benefits to the patient can therefore, from a ethical point of view, justify the possible disadvantages connected with the study in the form of the inconvenience of extra visits linked to MRI and slightly more frequent clinical and biochemical examinations than usual.

17 Adverse reactions, risks and disadvantages

There are no known adverse reactions in the short term or long-term adverse reactions connected with MRI, as long as the exclusion criteria are adhered to, irrespective of the type of scanner used or the strength of the magnetic field. Before inclusion in the study, contra-indications for MRI will be reviewed, including examination of normal renal function in the form of s-creatinine in the normal range (inclusion criterion).
During MR scanning, an i.v injection of 10-15 ml (0.1 mmol/kg body-weight) of the contrast agent Dotarem is administered (Dotarem belongs to the group of stable macrocyclic contrast agents). The injection is administered in the bend in the elbow as with conventional blood sampling. The contrast agent is not radioactive and only very rarely results in an allergic reaction. In a few cases a temporary sensation of heat and feeling of pain is experienced at the injection site. The patient's se-creatinine is also monitored before the MR scan is carried out (control blood tests). The MR scan is estimated to last around 45 minutes which experience has shown patients find an acceptable time-frame.

Conventional X-ray of hands, wrists and feet will be performed 3 times during the study period (at inclusion and once a year thereafter). X-ray of hands, wrists and feet exposes the patient to a radiation dose below 0.002 mSv, which is such a small radiation dose that the risk is considered negligible (Appendix 5. Guidelines on the use of ionising radiation in a biomedical research trial, Danish National Committee on Biomedical Research Ethics). In comparison, a 2-level X-ray examination of the lungs administers a radiation dose of 0.11 mSv. Furthermore, annual background radiation (ambient radiation from the earth and space) is estimated to be 3 mSv.
Apart from the X-ray of hands, wrists and feet at the time of inclusion (if < 12 months since last routine X-ray of hands, wrists and feet), X-RAY frequency is consistent with everyday clinical practice and the patient will not be exposed to increased amounts of radiation.
In the long term the potential benefits to RA patients in the form of more sensitive methods for monitoring disease activity and prognostication, which will lead to a better clinical and radiographic outcome, are deemed to be ethically responsible and to justify the risks, disadvantages and adverse reactions linked to the current study.

18 Patient information and consent

18.1 General participant information

The following information concerning trial subjects' rights in a biomedical research project (copy from the website of the Danish National Committee on Biomedical Research Ethics: "Before you decide – on being a subject in a medical trial") is attached to the written patient information.
The patient taking part in a biomedical research project must be informed that:

- participation in the research project is completely voluntary and can only occur after you have received both written and oral information on the research project and signed the declaration of consent

- the participant may withdraw his/her consent to participate and withdraw from the research project at any time by giving notification orally, in writing or by clear indication by other means. If consent is withdrawn, this does not affect the participant's right to current or future treatment or other rights.

- the participant has the right to take a family member, friend or acquaintance with him/her to the information interview.

- the participant has the right to take time to consider before signing the declaration of consent.

- information on the patient's state of health, other purely private factors and other confidential information that emerges in connection with the research project is subject to the obligation of confidentiality

- storage of information about the participant, including information from blood samples and tissue, is in accordance with the provisions of the Danish Act on the

Processing of Personal Data and the Danish Health Act.

- access to the trial protocols can be obtained in accordance with the provisions of the Danish Access to Public Administration Files Act. This means that the participant can access all documents relating to his/her own participation in the trial, apart from those containing commercially confidential information or confidential information about others.

- the patient is entitled to complain and receive compensation in accordance with the provisions of the Danish Act on the Right to Complain and Receive Compensation within the Health Service.

18.2 Guidelines for participant information in this study

The investigator is responsible for the provision of information, but information may be provided by any person with the technical competence to provide information on the research project and who is directly connected with this project, according to The Information Regulation. The guidelines shall apply to the person who in practice provides the information, i.e. the health professional responsible for information provision.

- The patient is informed of the opportunity to participate in connection with a control visits at the rheumatology outpatient clinic, at which they are informed that the issue under discussion is participation in a biomedical research project.

- Before the information interview, an agreement is reached on time and place

- The oral information is provided before the written information, or vice versa, depending on the participating departments' routines.

- After oral and written information has been provided, informed consent is obtained by the attending physician or by another doctor connected with the project.

- The participant is informed of the purpose and procedures, as well as possible risks, and any questions concerning the study are addressed.

- Information must be provided in easily accessible language without using technical or value-laden terms and must be given in a considerate manner, tailored to the recipient's individual situation with regard to age, maturity, experience, etc.

- It must be ensured that the information interview, which takes place in connection with the visit to the rheumatology outpatient clinic is not interrupted or suspended. If the trial participant has been asked about possible participation in the project at an outpatient visit or has subsequently been contacted by telephone, the trial participant will be asked, before the information interview, whether he/she has had sufficient time to consider participation in the project.

- The option of bringing a support person to the information interview must be made clear by offering the patient an extra information interview with a relative present, which is also mentioned in the information from the Ethics Committee (see Section 18.1), attached to the patient information.

- A minimum consideration time of one 24-hour period must be given between the provision of oral information and the obtaining of consent, which can be signed 1-2 days thereafter. However, the period between the provision of information and the obtaining of consent should not be disproportionately long.

- No advertising may be used as only patients subject to regular monitoring in the participating centres' rheumatology departments can participate.

- The declaration of informed consent must be read, signed and dated by the patient and the person obtaining consent before any screening procedures relating to the study are performed.

- The patient receives a signed copy of the consent declaration and the original is stored in the patient's medical records.

- A dated memorandum must be attached to the patient's source documents confirming that informed consent has been obtained prior to the start of study-related procedures, and that the patient has received a signed copy.

- The patient is assigned a contact doctor/nurse whom the patient can contact if he/she has any questions in connection with the project.

18.3 Information during the study

- The patient must be informed if, during implementation of the trial, any new information becomes available relating to efficacy, risks, adverse reactions, complications or disadvantages.

- All patients who continue to be active in the trial must be informed if the research project's study design is materially modified in relation to the patient's safety.

- The patient must be informed if, during implementation of the research project, any information becomes available relating to the patient's state of health, unless the patient has unequivocally expressed that he/she does not wish to be informed, c.f. Article 13 of the Information Regulation.

- When drawing up reports relating to the research project, the trial doctor or health professional responsible for information provision may inform the patient about the results obtained and about any possible consequences for the individual patient, providing this is practically possible and the patient wishes to receive this information.

19 Handling and archiving of data

At the conclusion of the research project, the data will be compiled in a database. All electronic CRFs are stored by the investigator in accordance with applicable regulations, i.e. for at least 10 years (see Section 15.1.7).

20 Reporting and distribution of data

The management body comprises the primary investigator (PI) and sponsor, Consultant Professor Kim Hørslev-Petersen M.D, DMSc, Gråsten Rheumatology Hospital, the co-PI, Consultant Professor Mikkel Østergaard M.D, PhD, DMSc, Department of Rheumatology RM, Glostrup Hospital, project leader, clinical assistant Dr. Signe Møller-Bisgaard M.D, Department of Rheumatology RM, Glostrup Hospital/Slagelse Hospital, Consultant Merete Lund Hetland M.D, PhD, Department of Rheumatology RM, Glostrup Hospital and Consultant Bo Ejbjerg Phd, Department of Rheumatology, Slagelse Hospital.
The Steering Committee and other co-investigators are persons who contribute materially to the project. The compiled data belongs to the investigators.
Manuscript drafts are drawn up be members of the management body and presented to the Steering Committee/co-investigators for comment and revision. The target for publication of the manuscripts is international English-language periodicals, with the project leader, PI and co-PI as the primary, secondary and tertiary authors, unless otherwise decided by the management body. In addition the participating departments attain co-authorship for every 12 patients who undertake the study, where the co-author also participates in the analysis and discussion of the results and the preparation of the article. Other persons who have contributed materially, including representatives from the Steering Committee, can become co-authors. In the event of disagreement the management body has the final decision.
Sub-projects in this protocol and possible supplementary projects can be analysed by the researchers responsible for these projects and published with one of these researchers as the primary author. Before this, a written agreement between the researchers, the management body, the Steering Committee and the co-investigators must be entered into. Other authorships relating to supplementary projects depend on the type of supplementary project. The sequence of authors must be described in the abovementioned written agreement and, apart from persons materially involved in the supplementary project, will usually include the investigators who contribute materially to the core project, including members of the management body. All sponsors will be mentioned as having supported the project in all publications. AbbVie Laboratories and any other sponsor will not be involved in data analysis or have any influence on the layout of manuscripts or abstracts. Manuscripts and abstracts will be presented to AbbVie at least 30 days prior to submission.

21 Publication plan

It is expected that it will be possible to submit an abstract to the American College of Rheumatology (ACR) congress/European League Against Rheumatism (EULAR) in 2015 and subsequent ACR/EULAR congresses. The aim is to publish the main study and sub-studies in renowned rheumatology periodicals, e.g. Arthritis & Rheumatism. Both positive and negative study results will be published. Publication will take place as soon as it is possible and

professionally responsible to do so, and in accordance with the Danish Act on the Processing of Personal Data.

22 Finance and insurance

The study is an investigator-initiated study. The study has been planned by a group of rheumatologists who asked AbbVie for financial support to carry out the project (see Section 22.1). The project leader, Signe Møller-Bisgaard, is employed as a research fellow up to and including September 2011 and thereafter has a position as clinical assistant at the Research Unit, Slagelse Hospital, to 31 December 2011. From January 2012 up to and including Dec. 2014, she is expected to be employed as a clinical assistant at the Research Unit, Slagelse Hospital in connection with enrolment as a PhD student at Copenhagen University. Thereafter, employment will be financed by other means.
The participants do not receive any remuneration but in specific cases travel expenses may be refunded. When approving the trial, the regional Biomedical Research Ethics Committee ensures that the patient is protected by an insurance and compensation scheme for trial subjects ("Before you decide…", patient guideline from Danish National Committee on Biomedical Research Ethics). Throughout the study period the patient is covered by the Danish Act on the Right to Complain and Receive Compensation within the Health Service.
The project group has previously received financial support from AbbVie Laboratories which produces Adalimumab, as well as from other firms producing biological medicines. None of the parties with primary responsibility for the study have any financial links to private firms, funds, etc. with an interest in the respective research project.

22.1 Support from AbbVie

AbbVie supports the project by supplying Adalimumab free of charge and by giving DKK 5,000,000 to cover expenses connected with implementation of the study (GCP monitoring, meeting activities, CRF design, implementation of the study programme, including clinical visits, biochemical and image diagnostic examinations, as well as data analysis, etc.). This amount is paid on an ongoing basis to the research account administered by the management body, out of which expenses connected with the project are paid. No personal honoraria are paid out. It is estimated that 35% of the amount goes to the wages of auxiliary personnel, GCP, statistics, etc., 20% to fees to the participating departments, 10% to biochemical analyses and 35% to procedures related to imaging.

Appendix A: **The 2010 ACR/EULAR classification criteria for rheumatoid arthritis**

The 2010 ACR/EULAR classification criteria for rheumatoid arthritis

	Score
Target population (Who should be tested?): Patients who • have at least 1 joint with definite clinical synovitis (swelling)* • with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement §	
1 large joint¶	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)#	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

* The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

† Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

‡ Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

§ Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

¶ "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

"Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

** In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).

†† Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anti-citrullinated protein antibody.

‡‡ Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

§§ Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

Appendix B: **1987 Criteria for the Classification of Acute Arthritis of Rheumatoid Arthritis**

1987 Criteria for the Classification of Acute Arthritis of Rheumatoid Arthritis

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3. Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

- For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 or these 7 criteria. Criteria 1 through 4 must have

been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is *not* to be made

Appendix C: **Identification of trial medicine**

Identification of trial medicine: Identification of Adalimumab

Investigational medicinal product	**Formula**	**Producer**
Adalimumab	SC injection 40 mg/0.8 ml	Abbott Laboratories

Packaging and labelling: The trial medicine will be delivered in filled dosage dispensing pens/syringes containing 40 mg Adalimumab. One box contains 2 filed dosage dispensing pens/syringes. The product labelling contains the following information:

- Primary investigator: Professor Kim Hørslev-Petersen
- Protocol name – IMAGINE
- Medication code number – X
- Medicinal product identification – Filled pens/syringes for subcutaneous injection
- Quantity of contents – 0.8 ml
- For clinical trial use only

In addition to the content of the pens/syringes, each pen/syringe is delivered in a dosing carton bearing the information:

- Contents – 2 filled injection pens/syringes
- Expiry date
- Blank field for noting the participant's identification number, initials and dispensing date
- Storage – Store at 2-8 C. Injection pen/syringe must be stored in the outer dosing carton. DO NOT FREEZE.
- Dosing instruction – in accordance with the investigator's instructions

Storage and application of the study medicine: The clinical supplies should be stored in the fridge at 2-8 C. Do not freeze and keep in a dark place. The clinical supplies are only for use in this trial, as specified in this protocol and must be stored in an appropriately secure environment under the conditions specified on the label, as described above. This storage regulations apply when delivering the study medicine to the trial subject or returning it to Abbott Laboratories.

Compliance: The investigator or his/her designee supplies the investigational medicinal product to trial participants only. The first dose (and where necessary the second) will be administered at the rheumatology department under supervision. Subsequent administrations can be administered outside the rheumatology department. To document compliance with the treatment, all filled and used injection pens/syringes must be counted and documented in the relevant CRF.

Medicinal product accounts: The investigator or his/her designee must confirm that the study medicine has been received intact and in the correct quantity. This must be documented by signing and dating a CSI (Clinical Supplies Invoice) or similar document. A careful and updated account must be maintained detailing the study medicine in the departments, i.e. CSI numbers, number of delivered and filled injection pens/syringes and date of delivery of the study medicine to the participant. All used and unused supplies are registered and

documented for Abbott Laboratories. The investigators undertake to not supply the study medicine to persons not included in the trial. All participating centres will store and updated overview of the study medicine which will be checked in connection with the conclusion of the study.
The patient will be assigned a 4-figure number (representing the centre and the patient). The patient's study number, date of birth and initials will be noted on the medicine packaging. The batch number of the medicine and the date of delivery to the patient will be documented in the CRF. Accounts of each patient's study medicine will also be maintained.

Appendix D: **Health Assessment Questionnaire**

HEALTH ASSESSMENT QUESTIONNAIRE!
Stanford University School of Medicine
Division of Immunology & Rheumatology

Name_____ **Date**_____

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty[0]	With SOME difficulty[1]	With MUCH difficulty[2]	UNABLE to do[3]
DRESSING & GROOMING				
Are you able to:				
-Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
-Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
-Stand up from a straight chair?	☐	☐	☐	☐
-Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
-Cut your meat?	☐	☐	☐	☐
-Lift a full cup or glass to your mo	☐	☐	☐	☐
-Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
-Walk outdoors on flat ground?	☐	☐	☐	☐
-Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

- ☐ Cane
- ☐ Walker
- ☐ Crutches
- ☐ Wheelchair
- ☐ Devices used for dressing (button hook, zip long-handled shoe horn, etc.)
- ☐ Built up or special utensils
- ☐ Special or built up chair
- ☐ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and Grooming	☐ Eating
☐ Arising	☐ Walking

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty [0]	With SOME difficulty [1]	With MUCH difficulty [2]	UNABLE to do [3]
HYGIENE				
Are you able to:				
-Wash and dry your body?	☐	☐	☐	☐
-Take a tub bath?	☐	☐	☐	☐
-Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
-Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
-Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
-Open car doors?	☐	☐	☐	☐
-Open jars which have been previously opened?	☐	☐	☐	☐
-Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
-Run errands and shop?	☐	☐	☐	☐
-Get in and out of a car?	☐	☐	☐	☐
-Do chores such as vacuuming or yardwork	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

- ☐ Raised toilet seat
- ☐ Bathtub seat
- ☐ Jar opener (for jars previously opened)
- ☐ Bathtub bar
- ☐ Long-handled appliances for reach
- ☐ Long-handled appliances in bathroom
- ☐ Other (Specify:)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene	☐ Gripping and opening things
☐ Reach	☐ Errands and chores

Appendix E: **SF-36 & EQ-5D**

SF-36 QUESTIONNAIRE

(1992 -- Medical Outcomes Trust)

Patient Name: _____ Date: _____

1. In general, would you say your health is: (circle one)
   Excellent Very good Good Fair Poor

2. Compared to one year ago, how would you rate your health in general now? (circle one)
   Much better now than one year ago.
   Somewhat better now than one year ago.
   About the same as one year ago.
   Somewhat worse than one year ago.
   Much worse than one year ago.

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (Mark each answer with an **X)**

ACTIVITIES	**Yes, Limited A Lot**	**Yes, Limited A Little**	**No, Not Limited At All**
a. **Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports			
b. **Moderate activities,** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
c. Lifting or carrying groceries			
d. Climbing **several** flights of stairs			
e. Climbing **one** flight of stairs			
f. Bending, kneeling or stooping			
g. Walking more than a mile			
h. Walking several blocks			
i. Walking one block			
j. Bathing or dressing yourself			

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Mark each answer with an **X)**

	YES	NO
a. Cut down on the **amount of time** you spent on work or other activities		
b. **Accomplished less** than you would like		
c. Were limited in the **kind** of work or other activities		
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)		

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (Mark each answer with an **X)**

	YES	NO
a. Cut down the **amount of time** you spent on work or other activities		
b. **Accomplished less** than you would like		
c. Didn't do work or other activities as **carefully** as usual		

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups? (circle one)

Not at all Slightly Moderately Quite a bit Extremely

7. How much bodily pain have you had during the past 4 weeks? (circle one)

None Very mild Mild Moderate Severe Very severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all A little bit Moderately Quite a bit Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks - (Mark each answer with an **X)**

	All of the Time	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
a. Did you feel full of pep?						
b. Have you been a very nervous person?						
c. Have you felt so down in the dumps that nothing could cheer you up?						
d. Have you felt calm and peaceful?						
e. Did you have a lot of energy?						
f. Have you felt downhearted and blue?						
g. Did you feel worn out?						
h. Have you been a happy person?						
i. Did you feel tired?						

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? (circle one)

All of the time Most of the time Some of the time A little of the time None of the time

11. How TRUE or FALSE is each of the following statements for you?

	Definitely True	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
a. I seem to get sick a little easier than other people					
b. I am as healthy as anybody I know					
c. I expect my health to get worse					
d. My health is excellent					

Health Questionnaire

English version for the UK (validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

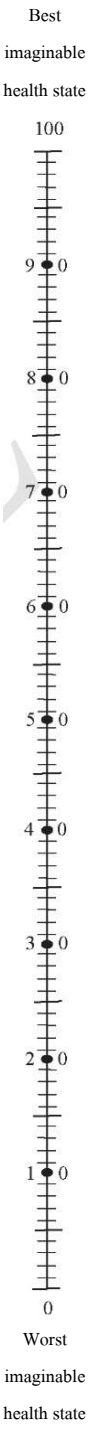
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix F: **DAS28**

DAS28-4(crp) = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*ln(CRP+1) + 0.014*GH + 0.96

Sqrt: square root
TJC: 28 Tender joint count
SJC: 28 Swollen joint count
CRP: C-reactive protein
GH: General Health on a 100mm. Visual Analogue Scale.

Appendix G: **The 2011 ACR/EULAR Definitions of Remission in Rheumatoid Arthritis Clinical Trials**

The 2011 ACR/EULAR Definitions of Remission in Rheumatoid Arthritis Clinical Trials

BOOLEAN-BASED DEFINITION:

At any time point, patient must satisfy all of the following:

Tender joint count ≤1†

Swollen joint count ≤1†

C-reactive protein ≤1 mg/dl

Patient global assessment ≤1 (on a 0–10 scale) ‡

INDEX-BASED DEFINITION:

Simplified Disease Activity Index score of ≤3.3§

† For tender and swollen joint counts, use of a 28-joint count may miss actively involved joints, especially in the feet and ankles, and it is preferable to include feet and ankles also when evaluating remission.

‡ For the assessment of remission we suggest the following format and wording for the global assessment questions. Format: a horizontal 10-cm visual analog or Likert scale with the best anchor and lowest score on the left side and the worst anchor and highest score on the right side. Wording of question and anchors: For patient global assessment, "Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?" (anchors: very well–very poor). For physician/assessor global assessment, "What is your assessment of the patient's current disease activity?" (anchors: none–extremely active).

§ Defined as the simple sum of the tender joint count (using 28 joints), swollen joint count (using 28 joints), patient global assessment (0–10 scale), physician global assessment (0–10 scale), and C-reactive protein level (mg/dl).

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Protocol Amendments

The protocol was subject to five protocol amendments during the study period. All amendments were prior to implementation approved by the scientific ethics committee.

Protocol amendment 1, 2 and implementation of the electronic randomisation procedure were implemented before inclusion of the first patient.

Protocol amendment 1
For later research purpose an extra diffusion weighted image (DWI) sequence was added for patients scanned at Herlev hospital and obtained at the same time as the already planned MRI scan.

Protocol amendment 2
Patients were asked to give blood and urine samples for bio-bank storage for later analysis. The blood and urine collection was scheduled to every 4 months at the same time as the already protocolled blood collection, ie. upon inclusion and after 4, 8, 12, 16, 20, and 24 months. This included 60 ml of blood per visit (whole blood for Pax-gene RNA tubes, blood to serum, EDTA plasma, citrate plasma and heparin plasma) and extra 20 ml whole blood in EDTA glass at the inclusion visit. The amount of urine was 10 ml per sample.

Protocol amendment 3
The randomisation procedure was changed from opening envelopes to that randomisation and allocation was done electronically in the electronic CRF (e-CRF).

The following section in the in the written participant information was changed from: “At the end of the trial after 2 year you can continue the medical treatment you recieve. The subsequent controls depends on your treatment and is planned by your doctor at your local hospital”. Changed to: “At the end of the trial after 2 year further medical treatment and subsequent controls are planned in collaboration with your doctor at your local hospital”.

Exclusion criteria concerning biologic pretests (serology for tuberculosis, hepatitis and x-ray examination of thorax) at the screeningvisit was changed. In connection with the screening visit, anamnesis regarding the patient's risk of hepatitis and tuberculosis was recorded. Biological pretests were only conducted on suspicion of tuberculosis and hepatitis and not as a standard procedure at the screening visit.

The allowed time interval for control blood samples (and ECG in connection with screening visits) ahead of the scheduled visits was changes from 5 up to 7 days.

Glucocorticoid administration was clarified. It was clarified that intraarticular glucocorticoid injections in clinically swollen joints was allowed despite DAS28-CRP below 3.2.

Clarification of methotrexate (MTX) dose escalation. It was clarified that dose escalation for patients alerady receiving MTX was 5mg/2 week to the maximum tolerated dose.

Protocol amendment 4

Køge Hospital was included as a recruiting center.

The time interval for the planned scheduled visits was extended to vary +/- 14 days instead of +/- 10 days.

Protocol amendment 5

The hospital Sygehus Vendsyssel at Hjørring was included as a recruiting center

Two additional treatment steps were added to the treatment algorithm. The treatment algorithm was change from containing 6 steps to contain 8 steps, since there was a potential risk that some patients would need two extra steps if treatment had to be intensified at baseline and at the following visits

The study was extended with an 8-year observational extension protocol: "Long-term efficacy of a 2 year MRI guided treatment strategy on disease activity, imaging progression, physical function and quality of life in patients with rheumatoid arthritis (RA) - Follow up study year 3, 4, 5 and 10 of the IMAGINE-RA cohort". Clinical and imaging examinations are carried out at year 3, 4, 5 and 10 from the patients baseline visit. The objective is to investigate whether an MRI-guided treatment strategy for two years, in patients with rheumatoid arthritis in low disease activity/remission, in the long term , over 10 years, can increase the rate of remission, prevent progression of erosive joint damage and lead to a better functional level and quality of life.

Statistical Analysis Plan (SAP)

Impact of a magnetic resonance imaging-guided treat-to-target strategy on disease activity and progression in patients with rheumatoid arthritis (the IMAGINE-RA trial): a multicentre randomised controlled trial

Version: 2.0 (November 9, 2017)
Author: Signe Møller-Bisgaard
Date: 9-NOV-2017

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Study synopsis

The IMAGINE-RA study was designed and run as a non-blinded, multicentre, 2-year, randomised controlled trial (RCT) with a parallel group design investigating whether an imaging based treat-to-target treatment strategy using MRI and DAS28 (Disease Activity Score involving 28 joints) could prevent progression of erosive joint damage and increase the remission rate in patients with RA compared to a treat-to-target treatment strategy guided only by DAS28**.**

The current/modern treatment strategy involves early and aggressive treatment with frequent clinical follow-up aiming at reaching a target of sustained clinical remission or low disease activity in patients with RA (Smolen et al. Ann Rheum Dis 2017;76(6), Smolen et al. Ann Rheum Dis 2010;69(6)). This treat to target strategy has been shown to slow the destructive progression and prevent functional loss. However, it has been demonstrated that 20-30% of patients, who reach the treatment target of clinical remission, still show progressive erosive joint damage, irrespective of what remission criteria are used (Lillegraven et al. Ann Rheum Dis 2012;71(5)). This demonstrates that better and more sensitive methods for prognostication and monitoring of the disease activity are needed. Bone Marrow Edema (BME)/osteitis, detected by magnetic resonance imaging (MRI) has proved to be an independent predictor of subsequent radiographic progression (Hetland et al. Ann Rheum Dis 2009;68(3), Gandjbakhch et al. Ann Rheum Dis 2011;70(12)). Guiding the treatment based on presence/absence of BME may therefore be clinically beneficial.

Study Objectives

All methods used in the IMAGINE study are described in the published protocol by Møller-Bisgaard et al (Møller-Bisgaard et al. Trials. 2015 Apr 21;16(1):178).

Primary outcomes

The IMAGINE trial has two co-primary outcome measures, a clinical and a radiographic outcome.

Clinical outcome:

The primary clinical outcome is achieving disease remission according to the disease activity score **(**DAS28-CRP) at 24 months. Achieving disease remission is defined as DAS28-CRP <2.6

- **The rationale for choosing DAS28-CRP as co-primary outcome was that** in daily clinical care, the disease activity is recommended to be monitored and treatment decisions to be based on a composite disease activity score. In daily clinical practice the Disease Activity Score (DAS28) (www.das-score.nl) is used. The score is calculated based on the physician's examination of 28 tender and swollen joints, laboratory assessment of an acute phase reactant, either C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) and the patient's assessment of global health on a visual analogue scale (VAS). The DAS score used in the IMAGINE study is calculated based on CRP:

$DAS28\text{-}4(crp) = 0.56*\sqrt{(TJC28)} + 0.28*\sqrt{(SJC28)} + 0.36*\ln(CRP+1) + 0.014*GH + 0.96$

TJC28: Tender joint count (0-28)

SJC28: Swollen joint count (0-28)
CRP: C-reactive protein (mg/L)
GH: General Health on a 100 mm Visual Analogue Scale (0-100)

Radiographic outcome:
The primary radiographic outcome is no radiographic progression after 2 years assessed by the Sharp/vdHeijde method from baseline to 24 months. Progression is defined as change in total Sharp/vdHeijde score>0.

- Progression of structural joint damage in daily clinical practice is assessed by conventional radiographs and qualitatively evaluated by a radiologist. The rationale for choosing the Sharp/vdHeijde score as primary radiographic outcome is that the quantitative Sharp/vdHeijde scoring system is the most widely used, most sensitive and validated quantitative scoring system used for evaluating structural joint damage in clinical trials (van der Heijde et al. Rheumatology 1999;38(10), van der Heijde et al. Best Pract Res Clin Rheumatol 2004;18(6)). The Sharp/vdHeijde scoring system includes scoring of erosion and joint space narrowing in predefined areas of the hands and feet, with total scores of 0-280 and 0-168, respectively, giving a total Sharp/vdHeijde score (TSS) of 0-448.

Secondary outcomes
The secondary objectives of this trial are to compare fulfilment of other remission criteria, status scores and change scores from baseline to 24 months follow-up in a range of clinical and imaging outcomes.

Key secondary outcome measures are listed below:

Clinical:
- Remission according to ACR/EULAR 2011 criteria assessed at 24 months, defined as
  - A patient must satisfy all of the following: TJC ≤1, SJC ≤1, CRP ≤1 mg/dL and patient global assessment (PGA) ≤1 (on a 0–10 scale)

- Simplified Disease Activity Index (SDAI) remission (SDAI ≤3.3) assessed at 24 months, defined as
  - SDAI= TJC (0-28) + SJC (0-28) + PGA (on a 0-10 scale) + evaluator global assessment (on a 0-10 scale) + CRP mg/dL (0-10)

- Clinical Disease Activity Index (CDAI) remission (CDAI ≤ 2.8) assessed at 24 months, defined as
  - CDAI = SJC(0-28) + TJC(0-28) + PGA(0-10) + evaluator global assessment (0-10)

- DAS28-CRP at 24 months
- Morning stiffness at 24 months
- Tender joint count (0-40) at 24 months
- Swollen joint count (0-40) at 24 months
- Patient visual analogue scale (VAS) global at 24 months
- Patient VAS pain at 24 months

- Patient VAS fatigue at 24 months
- Physician VAS global at 24 months

Radiographic:

- Change in Sharp/vdHeijde score from 0-24 months

MRI

- No progression in MRI erosions (RAMRIS) score from 0-24 months. Progression is defined as change in RAMRIS erosion score >1
- Change in MRI erosion (RAMRIS) score from 0-24 months
- MRI synovitis (RAMRIS) score at 24 months
- Change in MRI synovitis (RAMRIS) score from 0-24 months
- MRI osteitis (RAMRIS) score at 24 months
- Change in MRI osteitis (RAMRIS) score from 0-24 months

Function and quality of life:

- Health assessment questionnaire (HAQ) at 24 months
- Changes in HAQ from 0-24 months and the percentage of patient with normal function HAQ≤0.5 is calculated at 24 months
- Short form 36 item (SF-36) score at 24 months
- Changes in SF-36 score from 0-24 months
- EuroQuol-5 dimensions (EQ-5D) score at 24 months
- Changes in EQ-5D score from 0-24 months

Other secondary outcome measures to be assessed are listed below:

Disease activity:

- DAS28-CRP remission (DAS28-CRP<2.6) at 12 months
- Remission according to ACR/EULAR 2011 criteria assessed at 12 months
- SDAI remission (SDAI ≤3.3) assessed at 12 months
- CDAI remission (CDAI ≤ 2.8) assessed at 12 months
- DAS28-CRP at 12 months
- Morning stiffness at 12 months
- Tender joint count (0-40) at 12 months
- Swollen joint count (0-40) at 12 months
- Patient VAS global at 12 months
- Patient VAS pain at 12 months
- Patient VAS fatigue at 12 months
- Physician VAS global at 12 months

Radiographic:

- No radiographic progression from 0-12 and 12-24 months (assessed by the Sharp/vdHeijde method). Progression is defined as change in total SHS>0
- Change in Sharp/vdHeijde score from 0-12 and 12-24 months

MRI

- No progression in MRI erosions (RAMRIS) score from 0-12 and 12-24 months
- Change in MRI erosion (RAMRIS) score from 0-12 and 12-24 months
- MRI synovitis (RAMRIS) score at 12 months
- Change in MRI synovitis (RAMRIS) score 0-12 and 12-24
- MRI osteitis (RAMRIS) score at 12 months
- Change in MRI osteitis (RAMRIS) score 0-12 and 12-24

The IMAGINE study was planned in 2010 and the protocol written in 2011. In 2011 the OMERACT scoring system for assessing joint space narrowing (JSN) had been developed (Østergaard et al. J Rheumatol 2011, 38(9)) and in 2014 and 2015 validated (Glinatsi et al. J of Rheum 2015, 42(12), Døhn et al J Rheumatol 2014, 41(2)). A scoring system for MRI tenosynovitis has been developed and validated in 2017 (Glinatsi et al, J of Rheum may 2017, doi 10.3899/jrehum.161097 Epub aheas of print). Therefore the assessment of MRI JSN (RAMRIS) and tenosynovitis (RAMRIS) has been added as secondary outcome measures:

- MRI JSN (RAMRIS) at 12 and 24 months
- Change in MRI JSN (RAMRIS) score from 0-12, 12-24 and 0-24 months
- MRI tenosynovitis (RAMRIS) score at 12 and 24 months
- Change in MRI tenosynovitis (RAMRIS) score from 0-12, 12-24 and 0-24 months
- MRI total inflammation score (sum score of MRI synovitis, osteitis and tenosynovitis) score at 12 and 24 months
- Change in MRI total inflammation score (sum score of MRI synovitis, osteitis and tenosynovitis) score at 0-12, 12-24 and 0-24 months
- MRI total damage score (sum score of MRI synovitis, osteitis and tenosynovitis) score at 12 and 24 months
- Change in MRI total damage score (sum score of MRI synovitis, osteitis and tenosynovitis) score at 0-12, 12-24 and 0-24 months

Function and quality of life

- HAQ at 12 months
- Changes in HAQ from 0-12 months and the percentage of patient with normal function HAQ≤0.5 is calculated at 12 months
- SF-36 score at 12 months
- Changes in SF-36 score from 0-12 months measuring functional health as well as mental well-being
- EQ-5D score at 12 months
- Changes in EQ-5D score from 0-12 months

Explorative outcomes

Biomarkers

- Blood and urine samples have been stored in a biobank for later analysis of various biomarkers

Dynamic MRI

- Dynamic MRI sequences have been acquired for later analyses of dynamic MRI parameters (including initial rate of enhancement (IRE) and maximum enhancement (ME)

Description of the analysis of the pre-specified explorative outcome measures is beyond the scope of this analysis plan.

Study design

Sample size and power considerations:

Primary *clinical endpoint*: Assuming 60% of patients in the control group and 80% of patients in the intervention group reach the primary clinical endpoint (DAS<2.6) at month 24, a group size of 64 in each group is needed to give a statistical power of 80% (beta=0.20) for the detection of statistically 1-sided significant (p=0.05) treatment efficacy, assessed on the basis of two independent binomially distributed proportions using Pearson's chi-square statistics with a chi-square approximation with a 1-sided significance level of 0.05. Based on a specified group size of 100 patients in each group (200 in total), the project is assessed as having a 93% chance of success with regard to the clinical efficacy goal (statistical power 0.93).

Primary *radiographic endpoint* (assessed using the Sharp/vdHeijde score): Assuming that 75% of patients in the control group and 90% of patients in the intervention group reach the primary radiographic performance goal (no radiographic progression) at month 24, a group size of 79 in each group is required to give a power of 80% (beta=0.20) for detection of a statistically 1-sided significant (p=0.05) treatment efficacy, assessed on the basis of two independent binomially distributed proportions using Pearson's chi-square statistics with a chi-square approximation with a 1-sided significance level of 0.05. Based on the specified group size of 100 patients in each group (200 in total), the project is assessed as having an 88% chance of success with regard to the radiographic efficacy goal (statistical power 0.879).

Based on "sample size" estimation above, a total sample size of 200 RA patients was selected. All 200 patients were included from April 2012 (first patient's first visit) to June 2015 with the last patient's last visit in May 2017.

Statistical analysis methods

This section includes all the principal features of the proposed confirmatory analysis of the primary outcome(s) and the way in which anticipated analysis problems will be handled.

Primary Hypothesis Testing:

For the co-primary outcomes (DAS28 remission and no radiographic progression, respectively) the primary statistical test will be based on all usable data, irrespective of protocol deviations, on the basis of two independent binomially distributed proportions using Pearson's chi-square statistics with a chi-square approximation with a one-sided significance level of 0.05.

Estimation and Confidence Intervals:

The primary analysis on the co-primary outcomes (and other binary outcomes) assessed after 2 years will be conducted using repeated measures logistic regression models; adjusting for the original variable assessed at baseline (i.e. disease activity and Total Sharp Score, respectively). To preserve the statistical power the repeated measures design will be included

by modelling the trajectories over time with either a linear mixed effects model (continuous outcomes) or generalized linear mixed models (binary outcomes): Thus repeated measures mixed linear models will be used for the primary analyses, including participants as a random effect, with fixed factors for treatment arm (2 levels) and time point (6 levels for disease activity measures and 2 levels for the x-ray imaging outcomes), and the corresponding interaction (time×group), adjusted for the value at baseline.

Analysis sets

It is advantageous to demonstrate a lack of sensitivity of the principal trial results to alternative choices of the set of participants analysed. In a confirmatory trial - like the IMAGINE-RA trial – we plan to conduct both an analysis of the full analysis set (FAS) and a per protocol (PP) analysis, so that any differences between them can be the subject to explicit discussion and interpretation. In some cases, it may be desirable to plan further exploration of the sensitivity of conclusions to the choice of the set of participants analysed. In the IMAGINE-RA Trial, we will perform sensitivity analyses on two different enrolment (time) periods, corresponding to before (22 participants) and after registration on the www.clinicaltrials.gov website; the first mentioned period corresponds to approximately the first 3 months of inclusion. When the full analysis set, the per protocol set, and the analyses on the two different enrolment periods lead to essentially the same conclusions, confidence in the trial results is increased.

Full analysis set (FAS): The primary analyses will be based on the intention-to-treat population: All randomised participants exposed to at least the baseline assessment of any endpoint will be included. Participants in the FAS will be analysed according to randomised treatment (i.e. independent of adherence to protocol).

Per protocol analysis set (PP): The Per protocol analysis set includes all participants from the 'FAS' without significantly protocol deviations pre- or post-randomisation. Participants considered to have a protocol deviation will be:

- Any participant entering the study where inclusion criteria or exclusion criteria should have prevented entry

- Any participant not following the tight control regimen and treatment decision rules or other aspects of the protocol considered to potentially affect the efficacy results of the primary outcomes. The decision to exclude any participant or observation from the statistical analysis is a joint responsibility of the primary investigator, co-primary investigator, project leader, and the statistical advisor; the participants or observations to be excluded must be documented and signed by all parties, prior to database release. The documentation will be stored together with the remaining trial documentation.

- Any participant withdrawing or withdrawn during the study

All efficacy analyses will be based on the FAS. The PP analysis set will be used to explore the effect of good adherence etc. for the primary and secondary endpoints.

Missing values
Missing values represent a potential source of bias in a clinical trial. Hence, every effort was undertaken in the conduct of the IMAGINE-RA trial to fulfil all the requirements of the protocol concerning the collection and management of data (incl. the patients who did not adhere to the protocol). The inference from the IMAGINE-RA trial should be regarded as valid, none the less, provided that the various methods of dealing with missing values lead to essentially the same conclusions. Our primary analyses include all follow-up data (i.e. no data imputation to replace missing data).
With the repeated-measures mixed effects models (based on the repeatedly collected data on the same participant data from FAS) as the primary analysis approach, sensitivity analyses will be performed to assess the robustness of the primary endpoint analyses, including multiple-imputation (MI) analyses, using a model based approach for missing data. The primary MI analysis will be based on a "Markov chain Monte Carlo" (MCMC) simulation statement designed to fit Bayesian models to impute values for a data set with an arbitrary missing pattern, assuming a multivariate normal distribution for the data.
Both the statistical analysis based on the mixed effects (based on all usable data, and no manual imputation) and the MI approaches, assume that data are 'Missing at Random' (MAR) (Sterne JA, et al. BMJ. 2009;338:b2393), i.e. any systematic difference between the missing values and the observed values can be explained by differences in observed data. Possible analysis methods under a MAR assumption include mixed effects models and multiple imputation (White IR, BMJ 2011;342:d40).
However, MAR is often plausible if the reason for most missing data is shown to be administrative error but implausible if the reason is undocumented disease progression. In the case that MAR is implausible, the data is referred to as 'Missing not at random' (MNAR; i.e., even after the observed data are taken into account, systematic differences remain between the missing values and the observed values). We will also perform sensitivity analyses to explore the effect of departures from the MAR assumption made in the main analysis: these analyses will be done "worst-case" and "best-case" imputation in the event that data are MNAR (White IR, BMJ 2011;342:d40).

Manual imputation - worst case:

- **Disease remission according to the** disease activity score **(**DAS28-CRP): Missing data will be coded as a 0 (=no, not in remission)
- No radiographic progression after 2 years: Missing data will be coded as a 1 (=yes, progression since baseline)

Manual imputation - best case:

- **Disease remission according to the** disease activity score **(**DAS28-CRP): Missing data will be coded as a 1 (=yes, now in remission)
- No radiographic progression after 2 years: Missing data will be coded as a 0 (=no progression since baseline)

Checking model assumptions and outliers
To assess the adequacy of the linear models describing the observed data - and checking assumptions for the systematic and the random parts of the models - we will investigate the model features via the predicted values and the residuals; that is, the residuals have to be normally distributed (around 0) and be independent of the predicted values. Data points with

large residuals (potential outliers) and/or high leverage may distort the outcome and accuracy of a regression. Cook's distance measures the effect of deleting a given observation; Points with a large Cook's distance are considered to merit closer examination in the analysis. No explicit procedure (decision rule) for dealing with outliers was foreseen in the trial protocol; in case there is evidence to suggest that some outliers could have an impact on the primary analysis we will perform at least one other analysis eliminating or reducing the outlier effect and differences between their results will be discussed.

Statistical programming

The analyses will be conducted using SAS version 9.4 or newer and R version 3.3.3 or newer. For R, the package lme4 will be used (Bates D, Journal of Statistical Software; 67(1))

Anticipated outline of the study report (manuscript)

Figure1
CONSORT flow diagram

Table 1: Demographic and clinical baseline characteristics of participants in the IMAGINE-RA study presented by treatment group as well as the total.

Figure 2: Illustrating proportions responding over time for each group with 95% CI showing primary endpoints (delta TSS<0 and DAS28 remission 24 months), based on the Full Analysis Set.

Table 2: Full analysis set: Primary and secondary outcomes at 24 months following baseline; descriptive statistics will be applied for each group whereas the contrast between groups with 95%CI's will be based on Odds Ratios and Least Squares Means for categorical and continuous data, respectively.

Table 3: Per protocol set: Primary and secondary outcomes at 24 months following baseline; descriptive statistics will be applied for each group whereas the contrast between groups with 95%CI's will be based on Odds Ratios and Least Squares Means for categorical and continuous data, respectively.

Table 4: Safety data (Collected adverse events; full analysis set)

Appendix Table 1: Demographic and clinical baseline characteristics of participants in the IMAGINE-RA study presented by treatment group as well as the total. (Full Analysis Set: based on patients enrolled after the correct registration in www.clinicaltrials.gov).

Appendix Table 2: Primary and secondary outcomes at 24 months following baseline; descriptive statistics will be applied for each group whereas the contrast between groups with 95%CI's will be based on Odds Ratios and Least Squares Means for categorical and continuous data, respectively.
(Full Analysis Set: based on patients enrolled after the correct registration in www.clinicaltrials.gov).

Table 1: Demographic and clinical baseline characteristics of participants in the IMAGINE-RA study

	MRI tight control (n=)	Conventional tight control (n=)	All (n=)
Characteristic			
Women, n (%)			
Age, years			
Disease duration, years			
IgM RF positive, n (%)			
CRP, mg/L			
DAS28-CRP			
DAS28-CRP <2.6, n (%)			
SDAI			
CDAI			
Morning stiffness, min			
Tender joint count (0-40)			
Swollen joint count (0-40)			
Patient VAS global (0-100 mm)			
Patient VAS pain (0-100mm)			
Patient VAS fatigue (0-100 mm)			
Physician VAS (0-100 mm)			
van der Heijde modified Sharp score (0-448)			
MRI erosion			
MRI synovitis			
MRI bone marrow edema			
MRI bone marrow edema present, n (%)			
HAQ (0-3)			
Short F-36			
EuroQol-5 dimensions			
Treatment			
Step 1, n (%)			
Step 2a, n (%)			
Step 2b, n (%)			
NSAID stable dose, n (%)			
Prednisolone stable dose, n (%)			

Data will be presented as mean (SD) unless otherwise stated in the final table.

Table 2: Primary and secondary outcomes at 24 months based on the Full Analysis Set (FAS)

	MRI tight control (n=)	Conventional tight control (n=)	OR/difference (95% CI)	P value
Primary endpoints				
Radiographic: No radiographic progression at 24 months, n (%)				
Clinical: DAS28 remission at 24 months, n (%)				
Secondary endpoints				
Clinical				
ACR-EULAR boolean remission at 24 months, n (%)				
SDAI remission (SDAI<3.3) at 24 months				
CDAI remission at 24 months, n (%)				
DAS28-CRP at 24 months				
Morning stiffness at 24 months, min				
Tender joint count (0-40) at 24 months				
Swollen joint count (0-40) at 24 months				
Patient VAS global at 24 months				
Patient VAS pain at 24 months				
Patient VAS fatigue at 24 months				
Physician VAS global at 24 months				
Radiographic				
Change in TSS between 0-24 months				
MRI				
No progression in MRI erosion (RAMRIS) at 24 months, n (%)				
Change in erosion (RAMRIS) score between 0-24 months				
MRI synovitis (RAMRIS) score at 24 months				
Change in synovitis (RAMRIS) score between 0-24 months				
MRI osteitis (RAMRIS) score at 24 months				
Change in osteitis (RAMRIS) score between 0-24 months				
Function and quality of life				
HAQ at 24 months				
Change in HAQ from 0-24 months				
Patient with normal function (HAQ≤0.5), n (%) at 24 months				
SF-36 score at 24 months				
Change in SF-36 score from 0-24 months				
EQ-5D score at 24 months				
Change in EQ-5D score from 0-24 months				

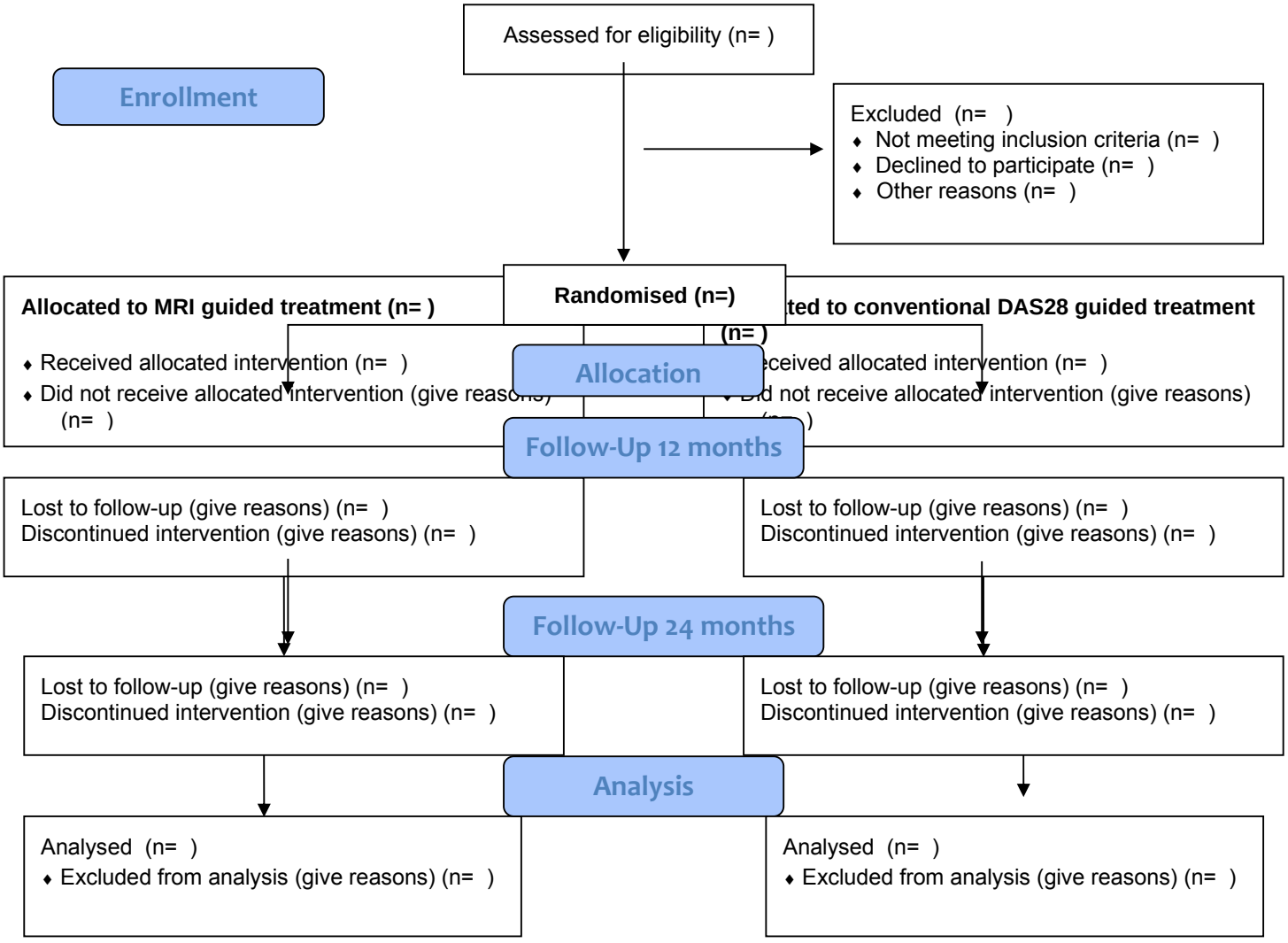
Table 3: Primary and secondary outcomes at 24 months based on the Per Protocol (PP) population

	MRI tight control (n=)	Conventional tight control (n=)	OR/difference (95% CI)	P value
Primary endpoints				
Radiographic: No radiographic progression at 24 months, n (%)				
Clinical: DAS28 remission at 24 months, n (%)				
Secondary endpoints				
Clinical				
ACR-EULAR boolean remission at 24 months, n (%)				
SDAI remission (SDAI<3.3) at 24 months				
CDAI remission at 24 months, n (%)				
DAS28-CRP at 24 months				
Morning stiffness at 24 months, min				
Tender joint count (0-40) at 24 months				
Swollen joint count (0-40) at 24 months				
Patient VAS global at 24 months				
Patient VAS pain at 24 months				
Patient VAS fatigue at 24 months				
Physician VAS global at 24 months				
Radiographic				
Change in TSS between 0-24 months				
MRI				
No progression in MRI erosion (RAMRIS) at 24 months, n (%)				
Change in erosion (RAMRIS) score between 0-24 months				
MRI synovitis (RAMRIS) score at 24 months				
Change in synovitis (RAMRIS) score between 0-24 months				
MRI osteitis (RAMRIS) score at 24 months				
Change in osteitis (RAMRIS) score between 0-24 months				
Function and quality of life				
HAQ at 24 months				
Change in HAQ from 0-24 months				
Patient with normal function (HAQ≤0.5), n (%) at 24 months				
SF-36 score at 24 months				
Change in SF-36 score from 0-24 months				
EQ-5D score at 24 months				
Change in EQ-5D score from 0-24 months				

Table 4: Safety data (collected adverse events)

	MRI tight control (n=)	Conventional tight control (n=)
Serious Adverse Events (SAE), n (%)		
Patients with serious infection, n (%)		
Cancer, n (%)		
Death, n (%)		
Discontinuation from the study due to AE, n (%)		

Figure 1: CONSORT flow diagram



Appendix Table 1: Demographic and clinical baseline characteristics of participants in the IMAGINE-RA study based on patients enrolled after the correct registration in www.clinicaltrials.gov

	MRI tight control (n=)	Conventional tight control (n=)	All (n=)
Characteristic			
Women, n (%)			
Age, years			
Disease duration, years			
IgM RF positive, n (%)			
CRP, mg/L			
DAS28-CRP			
DAS28-CRP <2.6, n (%)			
SDAI			
CDAI			
Morning stiffness, min			
Tender joint count (0-40)			
Swollen joint count (0-40)			
Patient VAS global (0-100 mm)			
Patient VAS pain (0-100mm)			
Patient VAS fatigue (0-100 mm)			
Physician VAS (0-100 mm)			
van der Heijde modified Sharp score (0-448)			
MRI erosion			
MRI synovitis			
MRI bone marrow edema			
MRI bone marrow edema present, n (%)			
HAQ (0-3)			
Short F-36			
EuroQol-5 dimensions			
Treatment			
Step 1, n (%)			
Step 2a, n (%)			
Step 2b, n (%)			
NSAID stable dose, n (%)			
Prednisolone stable dose, n (%)			

Appendix Table 2: Primary and secondary outcomes at 24 months based on the Full Analysis Set (FAS) of patients enrolled after the correct registration in www.clinicaltrials.gov

	MRI tight control (n=)	Conventional tight control (n=)	OR/difference (95% CI)	P value
Primary endpoints				
Radiographic: No radiographic progression at 24 months, n (%)				
Clinical: DAS28 remission at 24 months, n (%)				
Secondary endpoints				
Clinical				
ACR-EULAR boolean remission at 24 months, n (%)				
SDAI remission (SDAI<3.3) at 24 months				
CDAI remission at 24 months, n (%)				
DAS28-CRP at 24 months				
Morning stiffness at 24 months, min				
Tender joint count (0-40) at 24 months				
Swollen joint count (0-40) at 24 months				
Patient VAS global at 24 months				
Patient VAS pain at 24 months				
Patient VAS fatigue at 24 months				
Physician VAS global at 24 months				
Radiographic				
Change in TSS between 0-24 months				
MRI				
No progression in MRI erosion (RAMRIS) at 24 months, n (%)				
Change in erosion (RAMRIS) score between 0-24 months				
MRI synovitis (RAMRIS) score at 24 months				
Change in synovitis (RAMRIS) score between 0-24 months				
MRI osteitis (RAMRIS) score at 24 months				
Change in osteitis (RAMRIS) score between 0-24 months				
Function and quality of life				
HAQ at 24 months				
Change in HAQ from 0-24 months				
Patient with normal function (HAQ≤0.5), n (%) at 24 months				
SF-36 score at 24 months				
Change in SF-36 score from 0-24 months				
EQ-5D score at 24 months				
Change in EQ-5D score from 0-24 months				