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Comparing the effectiveness of our tailor-made management approach for rheumatoid arthritis with routine care from a clinical, patient, as well as economic point of view

Submission date
09/06/2020

Recruitment status
No longer recruiting

Registration date
27/10/2020

Overall study status
Completed

Last Edited
19/12/2025

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol
Background and study aims
Rheumatoid arthritis is a long-term condition that causes pain, swelling and stiffness in the joints. The condition usually affects the hands, feet and wrists. There may be periods where symptoms become worse, known as flare-ups or flares.
Current management recommendations still adopt a 'one-size-fits-all' treatment approach, where ideally, individualized treatment, or personalized medicine, is preferred. The prerequisite for precision medicine is the ability to classify individuals into groups that differ in their response to a specific treatment, which, for RA, still needs to be unravelled. However, we do believe that it is nowadays possible to individualize RA management by taking into account the presence of autoantibodies and the quick response to treatments such as glucocorticoids and targeted synthetic (ts)DMARDs.
Therefore, the aim of this project is to compare the effectiveness of our tailor-made management approach with routine care from a clinical, patient's as well as an economic point of view. In addition, we will investigate if our tailor-made management approach can be improved by adding biomarkers.

Who can participate?
Newly diagnosed, DMARD-naive, adult rheumatoid arthritis patients, according to the ACR /EULAR 2010 classification criteria

What does the study involve?
Patients will be assessed at baseline and at months 1, 2, 3, 4, 7, and 10.
Our tailor-made management approach is superior to routine care if treatment goals are attained faster without the use of more b- or tsDMARDs. The secondary outcome for the cost-effectiveness analysis will be the incremental cost-effectiveness ratio (ICER), which is the ratio of the difference in costs to incremental benefits between both management approaches.

Patients are randomized into routine care or our tailor-made approach.
Both management approaches use a treat-to-target strategy, aiming for low disease activity. In routine care medication can be intensified every 3 months, reflecting current daily practice.

What are the possible benefits and risks of participating?
All patients will receive active treatment for their recently diagnosed rheumatoid arthritis. Although all prescribed medication within this trial is approved and used according to label, patients can still experience side effects. Common side effects, which depend on the given medication, are pneumonia, sinusitis, pharyngitis, headache, abdominal pain, nausea, vomiting, anemia, leucopenia, neutropenia, elevated liver enzymes and injection site reactions.

Where is the study run from?
Erasmus Medical Center, Rotterdam (The Netherlands)

When is the study starting and how long is it expected to run for?
December 2019 to December 2025

Who is funding the study?
Alfasigma, Italy

Who is the main contact?
Dr. P.H.P. de Jong (p.h.p.dejong@erasmusmc.nl)

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2020-002802-21

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
PRIMERA001

Study information

Scientific Title
PeRsonalIzed MEdicine in Rheumatoid Arthritis (PRIMERA trial): a multicenter, single-blinded, randomized controlled trial comparing usual care with a tailor-made approach

Acronym
PRIMERA

Study objectives
Current study objectives as of 08/10/2025:
We hypothesize that treatment of RA can be individualized by taking into account the presence of autoantibodies and quick response to glucocorticoids and tsDMARDs. Therefore, the aims of this trial are:
1. To compare clinical effectiveness between our tailor-made management approach and routine care in newly diagnosed, DMARD-naive, rheumatoid arthritis patients, by looking at:
a. Proportion of patients using a b- or tsDMARD after 10 months of treatment.
b. Disease Activity Score (DAS) over time
Noteworthy is the fact that our tailor-made management approach is only superior to routine care if treatment goals are attained faster without the use of more b- or tsDMARDs
2. To evaluate the cost-effectiveness of our tailor-made treatment approach versus routine care, by using the incremental cost-effectiveness ratio (ICER) as outcome, which is the ratio of the difference in costs to incremental benefits between both management approaches
3. To evaluate if patient participation, satisfaction and compliance is increased with our tailor-made management approach compared to routine care
4. To explore whether our tailor-made management approach can be more individualized by adding biomarker(s)

Previous study objectives:
We hypothesize that treatment of RA can be individualized by taking into account the presence of autoantibodies and quick response to glucocorticoids and tsDMARDs. Therefore, the aims of this trial are:
1. To compare clinical effectiveness between our tailor-made management approach and routine care in newly diagnosed, DMARD naive, rheumatoid arthritis patients, by looking at:
a. Proportion of patients using a b- or tsDMARD after 9 months of treatment.
b. Disease Activity Score (DAS) over time
Noteworthy is the fact that our tailor-made management approach is only superior to routine care if treatment goals are attained faster without the use of more b- or tsDMARDs
2. To evaluate the cost-effectiveness of our tailor-made treatment approach versus routine care, by using the incremental cost-effectiveness ratio (ICER) as outcome, which is the ratio of the difference in costs to incremental benefits between both management approaches
3. To evaluate if patient participation, satisfaction and compliance is increased with our tailor-made management approach compared to routine care
4. To explore whether our tailor-made management approach can be more individualized by adding biomarker(s)

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 18/12/2020, Medisch Ethische Toetsings Commissie (METC) (Erasmus Medical Center, Dr. Molenwaterplein 40, Rotterdam, 3015 GD, Netherlands; +31 10 70 344 28; metc@erasmusmc.nl), ref: MEC-2020-0825

Study design
Multicenter single-blinded randomized controlled clinical trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Rheumatoid arthritis

Interventions
Current interventions as of 08/10/2025:
In this trial, the effectiveness of a tailor-made management approach is compared to routine care, from a clinical, patient, as well as an economic point of view, in patients with rheumatoid arthritis (RA).

Patients are randomized into routine care or our tailor-made approach using minimisation randomization stratified for center, by an independent call center.

In routine care, patients are initially treated with methotrexate(MTX) and glucocorticoids(GCs) once intramuscularly (im). The initial therapy of patients randomized to our tailor-made approach depends on the presence of autoantibodies. Patients without auto-antibodies will receive hydroxychloroquine(HCQ)+GCs im, while patients with auto-antibodies start with MTX+GCs im.

Both management approaches use a treat-to-target strategy, aiming for low disease activity (DAS ≤ 2.4). If DAS > 2.4, treatment is intensified until the aforementioned target is reached. In routine care, medication can be intensified every 3 months, reflecting current daily practice. The intensification steps are in the following order: (1) Triple DMARD therapy (TDT), consisting of MTX, sulfasalazine (SASP) and HCQ; (2) MTX + Filgotinib (FIL); (3) MTX + TNF inhibitor (TNFi); and (4) MTX + 2nd TNFi. In our tailor-made approach, besides the possible 3-monthly treatment intensification, medication alterations can also occur after 1 month and 4months, depending on the response to respectively GCs im and filgotinib (FIL). A good response to GCs im and FIL after respectively 1 and 4 months is defined as a DAS ≤ 2.4. The intensification steps in the tailor-made management approach are the same as routine care.

The prescribed medication within this trial is all approved and used according to the label. DMARD dosages are MTX 25 mg/week orally (week 1 15mg/week; week 2 20mg/week and week 3 and thereafter 25mg/week), SASP 2 g/day (week 1 500mg bid; week 2 500mg tid; and week 3 and thereafter 1000mg bid) and HCQ 400 mg/day. GCs are given once intramuscularly with either methylprednisolone 120mg or triamcinolone acetonide 80mg. Filgotinib is a once-daily oral therapy of 200mg. The TNFi, including adalimumab 40mg/2 weeks s.c; etanercept 50mg /week s.c; certolizumab pegol 200mg/2 weeks s.c(after loading doses of 400mg/2 weeks at week

0, 2 and 4).; golimumab 50mg/4 weeks s.c.; and infliximab 3-5mg/kg at week 0, 2and 6 and 8 weekly thereafter, is free of choice for the treating rheumatologist. Concurrent treatment with NSAIDs and intra-articular GC injections (maximum of 2 per 3 months) will be allowed during follow-up.

Previous interventions:
In this trial, the effectiveness of a tailor-made management approach is compared to routine care, from a clinical, patient, as well as an economic point of view, in patients with rheumatoid arthritis (RA).

Patients are randomized into routine care or our tailor-made approach using minimisation randomization stratified for center, by an independent call center.

In routine care, patients are initially treated with methotrexate(MTX) and glucocorticoids(GCs) once intramuscularly (im). The initial therapy of patients randomized to our tailor-made approach depends on the presence of autoantibodies. Patients without auto-antibodies will receive hydroxychloroquine(HCQ)+GCs im, while patients with auto-antibodies start with MTX+GCs im.

Both management approaches use a treat-to-target strategy, aiming for low disease activity (DAS<2.4). If DAS ≥2.4, treatment is intensified until the aforementioned target is reached. In routine care, medication can be intensified every 3 months, reflecting current daily practice. The intensification steps are in the following order: (1) Triple DMARD therapy (TDT), consisting of MTX, sulfasalazine (SASP) and HCQ; (2) MTX + Filgotinib (FIL); (3) MTX + TNF inhibitor (TNFi); and (4) MTX + 2nd TNFi. In our tailor-made approach, besides the possible 3-monthly treatment intensification, medication alterations can also occur after 1 month and 4months, depending on the response to respectively GCs im and filgotinib (FIL). A good response to GCs im and FIL after respectively 1 and 4 months is defined as a DAS <2.4 OR ΔDAS >0.6. The intensification steps in the tailor-made management approach are the same as routine care.

The prescribed medication within this trial is all approved and used according to the label. DMARD dosages are MTX 25 mg/week orally (week 1 15mg/week; week 2 20mg/week and week 3 and thereafter 25mg/week), SASP 2 g/day (week 1 500mg bid; week 2 500mg tid; and week 3 and thereafter 1000mg bid) and HCQ 400 mg/day. GCs are given once intramuscularly with either methylprednisolone 120mg or triamcinolone acetonide 80mg. Filgotinib is a once-daily oral therapy of 200mg. The TNFi, including adalimumab 40mg/2 weeks s.c; etanercept 50mg /week s.c; certolizumab pegol 200mg/2 weeks s.c(after loading doses of 400mg/2 weeks at week 0, 2 and 4).; golimumab 50mg/4 weeks s.c.; and infliximab 3-5mg/kg at week 0, 2and 6 and 8 weekly thereafter, is free of choice for the treating rheumatologist. Concurrent treatment with NSAIDs and intra-articular GC injections (maximum of 2 per 3 months) will be allowed during follow-up.

Intervention Type
Drug

Phase
Phase III/IV

Drug/device/biological/vaccine name(s)

csDMARDs, 1. Methotrexate, 2. Sulfasalazine, 3. Hydroxychloroquine, tsDMARDs, 4. Filgotinib, bDMARDs, 5. Etanercept, 6. Adalimumab, 7. Certolizumab pegol, 8. Golimumab, 9. Infliximab, Others, 10. Glucocorticoids, 11. NSAIDs i.e. naproxen, diclofenac, ibuprofen

Primary outcome(s)

Current primary outcome measures as of 08/10/2025:
Clinical effectiveness: Proportion of patients using a b- or tsDMARD after 10 months of treatment, measured using patient records at one timepoint

Previous primary outcome measures:
1. Clinical effectiveness:
1.1. Proportion of patients using a b- or tsDMARD after 10 months of treatment, measured using patient records
1.2. Disease activity, measured with the disease activity score (DAS) every 3 months with additional visits at months 1,2 and 4. (The DAS is a pooled index that involves the incorporation of a graded 53-joint count for tenderness (Ritchie Articular Index, RAI), a 44-joint count for swelling, erythrocyte sedimentation rate (ESR) and general health (GH, measured with a VAS 0 - 100mm) into a formula to obtain a numerical indicator of disease activity)

2. Cost-effectiveness:
2.1. Quality Adjusted Life Years (QALYs). QALYs are determined by calculating the area under the curve of dutch EuroQol questionnaire with 5 dimensions (EQ-5D) every 3 months with additional visits at months 1, 2 and 4
2.2. Total costs divided into direct and indirect costs:
2.2.1. Direct costs: Medication costs are calculated from doses reported in the patients' case records, valued according to the Dutch college of health insurance. Medical consumption, including duration of hospitalizations and admission diagnosis, are recorded every 3 months with the iMTA medical consumption questionnaire. We will use the Dutch average length of stay by diagnosis if the duration of hospitalization is unknown.
2.2.2. Worker productivity is measured with the WorkProductivity and Activity Impairment (WPAI) questionnaire, which includes presenteeism and absenteeism. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

Key secondary outcome(s))

Current secondary outcome measures as of 08/10/2025:
Secondary outcome measures
1. Disease activity over time, measured with the disease activity score (DAS). The DAS is a pooled index that involves the incorporation of a graded 53-joint count for tenderness (Ritchie Articular Index, RAI), a 44-joint count for swelling, erythrocyte sedimentation rate (ESR) and general health (GH, measured with a VAS 0 - 100mm) into a formula to obtain a numerical indicator of disease activity
2. Time to achieve low disease activity (LDA, disease activity score using 44 joints (DAS) ≤2.4)
3. Cost-effectiveness:
3.1. Quality Adjusted Life Years (QALYs). QALYs are determined by calculating the area under the curve of the Dutch EuroQol questionnaire with 5 dimensions (EQ-5D) every 3 months, with additional visits at months 1, 2 and 4
3.2. Total costs divided into direct and indirect costs:
3.2.1. Direct costs: Medication costs are calculated from doses reported in the patients' case records, valued according to the Dutch College of Health Insurance. Medical consumption, including duration of hospitalizations and admission diagnosis, is recorded every 3 months with

the iMTA medical consumption questionnaire. We will use the Dutch average length of stay by diagnosis if the duration of hospitalization is unknown.
3.2.2. Worker productivity is measured with the WorkProductivity and Activity Impairment (WPAI) questionnaire, which includes presenteeism and absenteeism. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.
4. Patient-reported outcomes (PROs) over time:
4.1. Functional ability, measured with the health assessment questionnaire (HAQ)
4.2. Quality of life, measured with the Dutch EuroQol questionnaire with 5 dimensions (EQ-5D) with 5 levels
4.3. Fatigue, measured with a visual analogue scale (VAS, 0 – 100 mm)
4.4. Pain, measured with a numeric rating scale (NRS, 0 – 10)
Exploratory outcome measures
1. Clinical outcomes:
1.1. Disease activity (states) at 10 months, measured with the DAS

2. Patient-reported outcomes (PROs):
2.1. Functional ability, measured with the health assessment questionnaire (HAQ)
2.2. Quality of life, measured with the Dutch EuroQol questionnaire with 5 dimensions (EQ-5D) with 5 levels
2.3. Fatigue, measured with a visual analogue scale (VAS, 0 – 100 mm)
2.4. Pain, measured with a numeric rating scale (NRS, 0 – 10), Generalized Pain Questionnaire (GPQ) and PainDetect questionnaire
2.5. Self-reported disease activity, measured with the Routine Assessment of Patient Index Data 3 (RAPID3)
2.6. Morning stiffness severity and duration, measured with an NRS (0 - 10).
2.7. General Health, measured with a visual analogue scale (VAS, 0 – 100 mm)
2.8. Patient satisfaction measured with the Treatment Satisfaction Questionnaire for Medication (TSQM) and VAS
2.9. Compliance measured with the Medication Adherence Report Scale (MARS-5)
2.10. Patient participation measured with the 9-Item Shared Decision Making Questionnaire (SDM-Q9)
2.11. Patient participation and autonomy were measured using the Impact on Participation and Autonomy questionnaire (IPAQ)
2.12. Worker productivity, measured with the Work Productivity and Activity Impairment (WPAI) questionnaire
3. Biomarker(s) (levels). Blood will be collected at the indicated time points, and inflammation markers will be measured using the Olink inflammation panel (92 proteins). In addition, immune pathway analysis will be performed on whole blood using RNAseq analysis.

Previous secondary outcome measures:
Patients will be assessed every 3 months with additional visits at months 1, 2 and 4. At each visit, patients will fill out all the abovementioned questionnaires online and are seen by the research nurse, who calculates the DAS. Additional blood samples will be taken at baseline and 1 month and only at 2, 3 and 4 months if DAS ≥2.4 at the previous visit.

1. Clinical outcomes:
1.1. Disease activity (states) at 10 months, measured with the DAS
1.2. Biomarker(s) (levels). Blood will be collected at the indicated time points and inflammation markers will be measured using the Olink inflammation panel (92 proteins). In addition, immune pathway analysis will be performed on whole blood using RNAseq analysis

2. Patient-reported outcomes (PROs):
2.1. Self-reported disease activity, measured with the Routine Assessment of Patient Index Data 3 (RAPID3)
2.2. Morning stiffness (severity and duration), measured with a 10-point Likert scale
2.3. General Health, measured with a visual analogue scale (VAS, 0 – 100 mm
2.4. Fatigue, measured with a visual analogue scale (VAS, 0 – 100 mm)
2.5. Pain, measured with a visual analogue scale (VAS, 0 – 100 mm)
2.6. Functional ability, measured with the health assessment questionnaire (HAQ)
2.7. Quality of life, measured with the 36-Item Short Form Health Survey(SF-36) and Dutch EuroQol questionnaire with 5 dimensions (EQ-5D) with 5 levels
2.6. Patient satisfaction measured with the Treatment Satisfaction Questionnaire for Medication (TSQM) and VAS
2.7. Compliance measured with the Medication Adherence Report Scale (MARS-5)
2.8. Patient participation measured with the 9-Item Shared Decision Making Questionnaire (SDM-Q9)
2.7. Patient participation and autonomy measured using the Impact on Participation and Autonomy questionnaire (IPAQ)

3. Societal outcomes
3.1. Worker productivity, measured with the Work Productivity and Activity Impairment (WPAI) questionnaire

Completion date
31/12/2025

Eligibility

Key inclusion criteria
Current key inclusion criteria as of 08/10/2025:

1. Newly diagnosed, DMARD-naive RA patients, according to the 2010 criteria
2. Age ≥18 years

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Previous key inclusion criteria:

1. Newly diagnosed, DMARD-naive RA patients, according to the 2010 criteria
2. Between 18 and 80 years of age
3. Female participants of childbearing potential and male participants whose partner is of childbearing potential must be willing to ensure that they or their partner use effective contraception during the trial and for 3 months thereafter, as in standard practice

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
99 years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current key exclusion criteria as of 08/10/2025:
1. Current or previous DMARD usage.
2. Systemic GC use within the 3 months prior to randomization.
3. Unable to understand, speak and write in Dutch.
4. (Relative) contraindications for study medication.
4.1. Recent infection or malignancy within the 3 months prior to inclusion.
4.2. Pregnancy or lactation.
4.3. Female patients of childbearing potential and male patients whose partner is of childbearing potential who are not willing to ensure that they or their partner use effective contraception during the trial and for 3 months thereafter.
4.4. History of clinically significant hepatic dysfunction, as indicated by abnormal liver function tests. At inclusion, any single parameter may not exceed 2 times the upper limit of normal.
4.5. History of renal injury, glomerulonephritis, subjects with 1 kidney or a glomerular filtration rate (GFR) < 30 ml/min.

Previous key inclusion criteria:
1. Current or previous treatment of arthritis with DMARDs
2. Glucocorticoids (GCs) in the 3 months prior to randomization
3. (Relative) contraindications for study medication:
3.1. Evidence of ongoing infectious or malignant process obtained within 3 months prior to screening and evaluated by a qualified health care professional
3.2. Pregnant or nursing (lactating) women
3.3. Female participants of child bearing potential and male participants whose partner is of child bearing potential who are not willing to ensure that they or their partner use effective contraception during the trial and for 3 months thereafter as in standard practice.
3.4. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFT) such as aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/ serum glutamic pyruvic transaminase (ALT /SGPT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria: Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out laboratory error
3.5. History of renal trauma, glomerulonephritis, or subjects with one kidney only, or a glomerular filtration rate (GFR) < 30 ml/min.
3.6. Other underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the Investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation

in an immunomodulatory therapy
4. Unable to understand, speak and write in Dutch

Date of first enrolment
09/04/2021

Date of final enrolment
06/05/2024

Locations

Countries of recruitment
Netherlands

Study participating centre
Erasmus Medical Center
Dr. Molewaterplein 40
Rotterdam
Netherlands
3015 GD

Study participating centre
Leiden University Medical Center
Albinusdreef 2
Leiden
Netherlands
2333 ZA

Study participating centre
Maasstad Hospital
Maasstadweg 21
Rotterdam
Netherlands
3079 DZ

Study participating centre
Franciscus Gasthuis & Vlietland
Kleiweg 500
Rotterdam
Netherlands
3045 PM

Study participating centre
Franciscus Gasthuis & Vlietland
Vlietlandplein 2
Schiedam
Netherlands
3118 JH

Study participating centre
Albert Schweitzer Hospital
Albert Schweitzerplaats 25
Dordrecht
Netherlands
3318 AT

Study participating centre
Amphia Hospital
Molengracht 21
Breda
Netherlands
4818 CK

Study participating centre
IJsselland Hospital
Prins Constantijnweg 2
Capelle aan den IJssel
Netherlands
2906 ZC

Study participating centre
Admiraal de Ruyter Hospital
's-Gravenpolderseweg 114
Goes
Netherlands
4462 RA

Study participating centre
Medisch Spectrum Twente
Koningstraat 1

Enschede
Netherlands
7512 KZ

Study participating centre
Reumazorg ZWN
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Roosendaal
Netherlands
4707 CH

Study participating centre
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Den Haag
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Sponsor information

Organisation
Erasmus University Medical Center

ROR
https://ror.org/018906e22

Funder(s)

Funder type
Industry

Funder Name
Alfasigma

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		18/12/2025	19/12/2025	Yes	No