



**Universiteit
Leiden**
The Netherlands

Effectiveness of longstanding exercise therapy compared with usual care for people with rheumatoid arthritis and severe functional limitations: a randomised controlled trial

Teuwen, M.M.H.; Weely, S.F.E. van; Vlieland, T.P.M.V.; Wissen, M.A.T. van; Peter, W.F.; Broeder, A.A. den; ... ; Gademan, M.G.J.

Citation

Teuwen, M. M. H., Weely, S. F. E. van, Vlieland, T. P. M. V., Wissen, M. A. T. van, Peter, W. F., Broeder, A. A. den, ... Gademan, M. G. J. (2024). Effectiveness of longstanding exercise therapy compared with usual care for people with rheumatoid arthritis and severe functional limitations: a randomised controlled trial. *Annals Of The Rheumatic Diseases*, 83(4), 437-445. doi:10.1136/ard-2023-224912

Version: Publisher's Version

License: [Creative Commons CC BY-NC 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/3748225>

Note: To cite this publication please use the final published version (if applicable).

CLINICAL SCIENCE

Effectiveness of longstanding exercise therapy compared with usual care for people with rheumatoid arthritis and severe functional limitations: a randomised controlled trial

Max M H Teuwen ¹, Salima F E van Weely ¹, Thea P M Vliet Vlieland ¹,
 Maria A T van Wissen ¹, Wilfred F Peter ¹, Alfons A den Broeder,²
 Dirkjan van Schaardenburg ³, Wilbert B van den Hout ⁴,
 Cornelia H M Van den Ende ^{5,6}, Maaïke G J Gademan ^{1,7}

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/ard-2023-224912>).

For numbered affiliations see end of article.

Correspondence to

Max M H Teuwen, Orthopaedics, Rehabilitation and Physical Therapy, Leiden University Medical Center, Leiden, 2300 RC, The Netherlands; m.m.h.teuwen@lumc.nl

Received 24 August 2023
 Accepted 12 December 2023
 Published Online First
 3 January 2024



© Author(s) (or their employer(s)) 2024. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Teuwen MMH, van Weely SFE, Vliet Vlieland TPM, et al. *Ann Rheum Dis* 2024;**83**:437–445.

ABSTRACT

Objectives To compare the effectiveness of longstanding (>52 weeks), supervised exercise therapy with usual care in adults with rheumatoid arthritis (RA) and severe functional limitations.

Methods Participants were randomised 1:1 to the intervention (individualised goal-setting, active exercises, education and self-management regarding physical activity) or usual care. Primary endpoint was the change in the Patient-Specific Complaints activity ranked 1 (PSC1, 0–10) at 52 weeks. Secondary endpoints included the PSC activities ranked 2 and 3 (PSC2, PSC3), Health Assessment Questionnaire-Disability Index (HAQ-DI), Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL), 6-minute walk test (6MWT), Patient Reported Outcome Measurement Information System Physical Function-10 (PROMIS PF-10) and the Short Form-36 Physical and Mental Component Summary Scales (SF-36 PCS and MCS). (Serious) Adverse events (AEs) were recorded. Measurements were done by blinded assessors. Analyses at 52 weeks were based on the intention-to-treat principle.

Results In total, 217 people (90% female, age 58.8 (SD 12.9) years) were randomised (n=104 intervention, n=98 usual care available for analyses). At 52 weeks, the improvement of the PSC1 was significantly larger in the intervention group (mean difference (95% CI) –1.7 (–2.4, –1.0)). Except for the SF-36 MCS, all secondary outcomes showed significantly greater improvements favouring the intervention (PSC2 –1.8 (–2.4, –1.1), PSC3 –1.7 (–2.4, –1.0), PROMIS PF-10 +3.09 (1.80, 4.38), HAQ-DI –0.17 (–0.29, –0.06), RAQoL –2.03 (–3.39, –0.69), SF-36 PCS +3.83 (1.49, 6.17) and 6MWT +56 (38, 75) m). One mild, transient AE occurred in the intervention group.

Conclusion Longstanding, supervised exercise therapy was more effective than usual care in people with RA and severe functional limitations.

Trial registration number Netherlands Trial Register (NL8235), included in the International Clinical Trial Registry Platform (<https://trialsearch.who.int/Trial2.aspx?TrialID=NL8235>).

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Exercise therapy is a proven effective and recommended treatment for rheumatoid arthritis (RA), with beneficial effects on aerobic capacity, muscle strength, functional ability and quality of life.
- ⇒ The evidence was so far gathered in patients with RA with stable disease and no or few comorbidities.

WHAT THIS STUDY ADDS

- ⇒ This study is the first evaluation of a personalised, longstanding, supervised exercise therapy programme in patients with RA with severe disability due to persisting disease activity, joint damage and/or comorbidities.
- ⇒ The exercise programme was tailored to individual functional limitations, delivered by trained physical therapists in primary care and had a duration of ≥52 weeks.
- ⇒ At 52 weeks, the longstanding exercise therapy programme was more effective than usual care with respect to functional ability and physical quality of life.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ In people with RA and severe functional limitations, the provision of personalised, longstanding, supervised exercise therapy should be considered.
- ⇒ For future implementation, education of physical therapists on the tailored approach and focus on active treatment modalities is needed.
- ⇒ Further research into the cost-effectiveness of personalised, longstanding, supervised exercise therapy in the treatment of RA is warranted.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic disease, mainly characterised by arthritis of the peripheral joints, globally affecting about 0.2–0.5% of the population, and women more

often than men (ratio 2.5:1).^{1,2} Pharmacological treatment strategies for RA have drastically improved over the last decades. Currently, a minority of patients with RA are having unsatisfactory control of disease activity, as illustrated by the 5–20% of patients with RA³ fulfilling the criteria for difficult-to-treat (D2T) RA^{4,5} in clinical studies. Also, the consequences in terms of pain, fatigue, and physical and mental function, which can all adversely affect the execution of daily activities and participation in society, including the ability to work, are substantial in some patients.^{6–8} Regarding functional disability specifically, an association with disease activity has been established,^{9–11} but it can also be related to other factors such as joint damage or deformities, complications of the disease or its treatment and/or comorbidity.^{10,11}

Patients with RA and functional disability may benefit from exercise therapy. Indeed, in clinical guidelines on the management of RA, exercise therapy is recommended in addition to pharmacological treatment.^{12–14} This recommendation is based on the ample evidence for the benefits of exercise programmes as an effective and safe intervention, improving aerobic capacity, muscle strength and functional ability of patients with RA.^{15–18}

Regarding the evidence on the effectiveness of exercise therapy in RA, it must be noted that studies were generally done in highly selected patients,¹⁸ with a relatively favourable health status and stable, well-controlled disease activity. Patients with persistent disease activity, considerable joint damage, multiple joint replacements and/or comorbidities are therefore under-represented in research. This is striking, as in particular, patients in this subgroup may have severe limitations in daily activities and/or social participation and are putatively in need of exercise therapy, most likely of longer duration due to fluctuations of health status over time. We identified only one randomised controlled trial (RCT) that specifically included people with RA and active disease.¹⁹ That study was executed during admission for inpatient multidisciplinary rehabilitation, with average duration of 30 days.¹⁹ It showed a beneficial effect of dynamic exercise therapy on disease activity and muscle strength as compared with conventional exercises. Given the specific setting of that intervention, and the fact that the study was performed more than 25 years ago, its results may not be generalisable to the population of patients with RA and severe functional disability in the era of biological therapy.

The health status of current patients with RA and severe functional disability may be complex, and so may be the tailoring of treatment. Although personalisation is a core competency of health professionals in rheumatology²⁰ and underlined in a recent physical therapy guideline on the management of RA,²¹ a specific approach for the personalisation of treatment may be needed in complex cases. Examples of such approaches that are proven effective include a tailored exercise intervention for elderly people with mobility problems^{22,23} and for patients with knee osteoarthritis and multimorbidity.²⁴ In patients with RA and severe functional disability, the effectiveness of such a systematic, comprehensive approach has not yet been established.

In conclusion, there is a lack of studies on exercise therapy for people with RA with severe functional disability, using a specific, personalised approach. The Longstanding-EXercise Therapy in people with RA (L-EXTRA) Study was designed to evaluate the effectiveness of a 52-week, personalised, supervised exercise therapy programme compared with usual care in a population of patients with RA with severe functional limitations in daily activities and/or participation.

METHODS

Study design

The L-EXTRA Study was conducted in parallel with a similar study in people with axial spondyloarthritis. The protocol of both studies was published earlier.²⁵ It concerns a 52-week, randomised, assessor-blinded, parallel-group study, with follow-up assessments at 104 or 156 weeks. The study was registered in the Netherlands Trial Register, within the International Clinical Trials Registry Platform (NL8235). This paper presents the 52-week results.

Patient and public involvement

Online supplemental table 1 shows the involvement of patients in the study.²⁶ Two patient representatives from the Dutch Arthritis Society (ReumaNederland) were involved in the identification of the research need, the design and conduct of the study. In addition, representatives from local or regional patient organisations actively supported the recruitment of patients.

Participants

Eligible individuals were adults (aged ≥ 18 years) with a clinical diagnosis of RA made by a rheumatologist. Individuals had self-perceived severe limitations in daily activities involving self-care (eg, dressing, washing), and/or transfers (eg, getting in and out of bed, rising from a chair or using the toilet), and/or mobility indoors or outdoors. The limitations were directly or indirectly related to the rheumatic condition, for example, caused by persisting or progressive disease activity despite optimal medical treatment and/or severe joint damage and/or deformities and/or severe comorbidity, for example, pulmonary or cardiovascular disease. Moreover, their functional limitations were judged to be unlikely to improve or resolve with a brief exercise therapy intervention. Individuals who had received physical therapy in the past 3 months, either or not in the context of a multidisciplinary team intervention or were shortly in need of admission to a hospital or rehabilitation centre, were excluded.

Randomisation

Participants were randomised (1:1) to receive either long-standing, personalised exercise therapy or usual care for 52 weeks using randomisation software Castor Electronic Data Capture (Amsterdam, The Netherlands, 2019). Randomisation was stratified by sex (female/male) and healthcare insurance coverage of physical therapy (< 12 or ≥ 12 sessions) and executed in blocks of varying sizes of 4, 6 or 8. The latter was done to ensure a relatively equal distribution of intervention and usual care for patients over the study period. The two researchers carrying out the randomisation (WFP, SFEvW) were not involved in the data collection.

Recruitment and selection procedures

During the recruitment period of 22 months (planned 19 months plus 3 months elongation due to the COVID-19 pandemic), information on the study was continuously disseminated via various channels. The information was tailored to the target groups of people with RA (websites, digital newsletters, flyers and (digital) posters) and of rheumatologists and clinical nurse specialists (emails, digital and face-to-face presentations). In addition, information letters were sent by regular mail to selected groups of possibly eligible patients with RA in two centres (Reade, Amsterdam; Sint Maartenskliniek, Nijmegen). Individuals could express their interest in the study by online self-registration or registration via their treating clinician. Screening of the eligibility

criteria (except for the clinical diagnosis of RA) was done by one of the researchers via a telephone interview and subsequently all screening results were discussed with two other members of the research team. In case of doubt, the larger research team was consulted and/or the patient and/or the treating rheumatologist were contacted. Finally, if patients fulfilled the eligibility criteria until then, the treating rheumatologist was asked to confirm the diagnosis of RA. Individuals meeting all eligibility criteria and providing written informed consent were enrolled.

After definite enrolment, the treating rheumatologist was asked to provide the following clinical information: rheumatoid factor positive (yes/no); anti-citrullinated protein antibodies positive (yes/no); the most recent Disease Activity Score (DAS-28)^{27 28} and fulfilment of the accepted definition of D2T RA (yes/no).^{4 5}

Intervention and usual care conditions

The intervention consisted of personalised, supervised and longstanding (≥ 52 weeks) active exercise therapy according to a standardised treatment protocol to be delivered by a trained primary care physical therapist (PT). The characteristics of the intervention are systematically described according to an established checklist²⁹ in online supplemental table 2. The intervention followed the framework of the WHO International Classification of Functioning, Disability and Health (ICF)³⁰ and the Hypothesis Oriented Algorithm for Clinicians-II^{31 32} and was based on similar approaches employed in previous research.^{22–24} It comprised an initial assessment, setting of treatment goals³³ regarding functional ability and provision of active treatment with regular monitoring and evaluation.

Active treatment comprised exercises (aerobic, muscle strengthening, flexibility/joint range of motion and functional/neuromotor exercises), patient education and the promotion of physical activity, including the provision of a simple waist pedometer. PTs tailored the intervention to the patient's functional limitations and overall health status, while for exercises carefully taking the guidelines for the adequate dosage into account.^{16 34 35} To ensure that all patients would receive an appropriately dosed intervention, a fixed frequency of two sessions per week for the first 12 weeks was set, whereafter it was advised to decrease the frequency to once weekly (total 64 sessions), with 14 additional optional sessions, depending on the participants' needs. If participants expressed the intention to use conventional physical therapy in addition to the intervention, this was discouraged.

The treating primary care PTs were primarily recruited through a national network of PTs with specific expertise regarding rheumatic diseases (www.reumanet.nl, accessed 22 October 2023). In case there was no member in the patient's residence, a PT working in the neighbourhood, preferably with expertise regarding the treatment of people with rheumatic diseases, was approached. Participating PTs took part in a mandatory training programme that was provided via a live, online training session or e-learning via an app (2.5 hours). They all received a manual and could seek guidance from an expert PT through video consultations or email. PTs trained to deliver the intervention were instructed not to treat people allocated to the usual care condition.

Participants randomised to the control group received usual care, with the content and delivery determined by the treating clinician(s) and participants themselves. The use of regular physical therapy, accessible through referral by a physician or self-referral (direct access), was neither encouraged nor discouraged. After 52 weeks, both participants in the intervention and usual

care groups had access to the intervention until the end of the study.

Outcome measures

The selection of outcome measures (see online supplemental table 3A) was primarily based on their ability to reflect functional ability on the level of the ICF component 'Activities and Participation'.³⁰ It was anticipated that the impact of potential underlying impairments on the level of 'Body Functions and Structures' such as pain, fatigue or muscle weakness would vary largely across individuals, so measures for such aspects were considered less suitable as outcomes on the group level. The primary endpoint was the change in the highest-ranked Patient-Specific Complaints Numerical Rating Scale (PSC1 NRS) score^{36 37} at 52 weeks. The PSC consists of the participant's three most limited activities, ranked from 1 to 3, with the level of difficulty of each activity scored on an NRS (anchors 0: easy; 10: impossible to do). Secondary endpoints included the PSC activities ranked second and third (PSC2 and PSC3), the Patient Reported Outcome Measurement Information System (PROMIS) Physical Function (PF)-10,^{38 39} the Health Assessment Questionnaire-Disability Index (HAQ-DI),^{40–42} the Rheumatoid Arthritis Quality of Life (RAQoL) Questionnaire,⁴³ the 36-Item Short-Form Health Survey (SF-36) Physical and Mental Component Summary Scales (PCS and MCS),^{44 45} and the 6-minute walk test (6MWT).⁴⁶

The occurrence of serious adverse events (SAEs) or adverse events (AEs) was prospectively recorded in the intervention group by the treating PTs. For the purpose of this study, SAEs were defined as occurrences resulting in death or being life-threatening, requiring hospitalisation or resulting in significant or permanent (aggravation of) disability or incapacity and being directly related to the exercise therapy treatment. AEs were defined as unfavourable occurrences directly related to exercise therapy treatment but were not severe, such as a temporary interruption of the therapy for nausea or a fall without injuries. At 52 weeks, participants in the intervention group who had used the intervention and participants in the usual care group who had used physical therapy were asked to complete four questions on two common AEs related to exercise or physical therapy treatment: occurrence of muscle soreness (yes/no) and/or fatigue (yes/no) and, if yes, a rating of severity on a scale from 0 to 10 (0=no–10=severe muscle soreness/fatigue).

Data collection and blinding

Online supplemental table 3B shows an overview of the time points of data collection. All outcomes were collected at baseline, 26 and 52 weeks, except for the PSC NRS and the 6MWT. The PSC NRS was not administered at 26 weeks, as we anticipated that this could trigger patients in the usual care group to seek help from a PT, thereby decreasing the contrast between the study arms. The 6MWT was not administered at 26 weeks for logistic reasons. All data were collected by two assessors (MMHT and MATvW), who were blinded to the treatment allocation. All outcomes other than the PSC NRS and 6MWT were electronically collected using the data monitoring system OnlinePROMs (2020, Interactive Studios). Throughout the conduct of the trial, measures were taken to preserve blinding. The patients were instructed repeatedly not to discuss their treatment allocation with the assessor and were given advice on how to avoid unblinding. The blinding failed in 29 of the 204 participants who completed the 52-week assessment (14%). For

120 of the remaining 175 participants (69%), the assessors were able to guess the treatment allocation correctly at 52 weeks.

Statistical analyses

A planned sample of 172 participants was estimated to provide >90% power for testing the superiority of the longstanding, personalised exercise intervention versus usual care for the primary endpoint of the PSC at week 52. The assumed difference was based on a population effect size of 0.5, being an accepted threshold for discrimination for changes in patient-reported outcomes in chronic diseases.⁴⁷ Power estimations were calculated using a two-sided significance level of 0.05. Taking into account a 20% drop-out rate, 215 people with RA and severe functional limitations needed to be included.

Analyses of effectiveness were performed according to the intention-to-treat principle, with the allocation only being revealed after all analyses were completed. Only measurements that had been performed within a time frame of 6 weeks around the initially planned time points were used for the analyses. As baseline covariates were balanced, the analyses were performed without adjustments. For the primary outcome PSC (NRS 1) as well for the PSC NRS 2 and 3 and the 6MWT, the mean changes between baseline and 52 weeks between the intervention and usual care groups were compared with unpaired Student's *t*-test. The results were expressed as mean difference between change scores with the 95% CI. For the other secondary outcomes, linear mixed models were employed as three time points were available for these outcomes and differences between the groups at these time points were estimated.

In addition, the effect size of the difference in change of the primary and secondary outcome measures between the two groups was determined using Cohen's $d = \frac{\text{mean difference intervention group} - \text{mean difference usual care group}}{\text{pooled SD}}$, the latter calculated with the formula: $SD = \sqrt{[(SD1^2 + SD2^2)/2]}$. Calculations were identical for all outcome measures.

We did not perform the originally planned per-protocol analysis. In the intervention group, the number of attended treatment sessions was, among other factors, likely to be related to the speed of achievement of their individual goals rather than treatment adherence. In the usual care group, there could be several reasons for either or not using conventional physical therapy, including the participant's health status or insurance, hampering the interpretation of findings.

RESULTS

Patient recruitment, randomisation and baseline characteristics

A total of 394 individuals were screened for eligibility, of whom 217 fulfilled the eligibility criteria, were willing to participate and were randomly assigned to receive longstanding personalised exercise therapy or usual care. Fifty-two of the total of 217 included patients (24%) had been recruited via the targeted information mailing to 593 patients in two centres. After randomisation, one participant in each group immediately withdrew; these patients were substituted to reach the intended number of 215 participants, resulting in 109 and 106 patients in the intervention and usual care groups (figure 1). There were 11 participants lost to follow-up between baseline and 52 weeks, whereas from two patients, the assessments at 52 weeks were not carried out within the appropriate time frame, so data from 104 (95%) and 98 (92%) participants in the intervention and usual care groups were available for the primary analysis. Regarding the participants lost to follow-up, three patients were deceased: two

in the intervention group and one in the usual care group, while others discontinued participation due to serious deterioration of health other than RA, private circumstances, lack of interest or lost contact.

Baseline demographic and disease characteristics were balanced between the intervention and usual care groups (table 1). The proportion of female patients (90%) was relatively high given the sex distribution of RA. The mean HAQ-DI of 1.7 (SD 0.5) in both groups, and the proportions of 43.6% and 51.1% of patients fulfilling the definition of D2T RA in the intervention and usual care groups are reflective of a population of people with RA and considerable functional disability. In general, the patients' disease activity seemed relatively well controlled, with a mean DAS-28 around the low disease activity threshold.²⁸ In addition, more than 95% had one or more comorbidities and around one-third of the participants had at least one joint arthroplasty.

Effectiveness

In total, 102 PTs were trained to deliver the intervention to the 109 patients in the intervention group. One-hundred and four (95%) patients started the intervention, whereas for 99 of these, the PT's records were sufficiently complete, showing that they used on average 39 sessions (SD 15.9). There were seven, six and nine patients who discontinued treatment between 13 and 26 weeks, 26 and 39 weeks, and 40 and 52 weeks, respectively, and who did not resume treatment before 52 weeks. Due to a logistical error, two patients (2%) in the usual care group were given access to the intervention and their PTs followed the mandatory training. One of these patients had 6 sessions and the other 32 sessions. In addition, 70 (66%) patients in the usual care group used physical therapy other than the study intervention during the 52-week study period.

Tables 2 and 3 present the results of the primary and secondary outcome measures.

Primary outcome measure

At week 52, the change from baseline of the PSC1 NRS was statistically significantly greater in the intervention than in the usual care group (mean difference -1.7 (95% CI -2.4 to -1.0)). The between-group effect size of the PSC1 NRS at 52 weeks was 0.7.

Secondary outcome measures

Similar to the PSC1 NRS, the differences in the change scores of the PSC2 NRS (mean difference -1.8 (95% CI: -2.4 to -1.1)), the PSC3 NRS (mean difference -1.7 (95% CI -2.4 to -1.0) and the 6MWT (mean difference 56 (95% CI 38 to 75) m) reached statistical significance at 52 weeks. Effect sizes were 0.7 and 0.8 for PSC2 and PSC3 NRS and 0.9 for the 6MWT.

The results for the outcome measures that were obtained at baseline, 26 and 52 weeks are presented in table 3. The improvement was statistically significantly greater in the intervention than the usual care group for the PROMIS PF-10, HAQ-DI, the RAQoL and the SF-36 PCS, while there were no differences regarding the changes of the SF-36 MCS.

The between-group effect sizes were 0.6 for the PROMIS PF-10, 0.5 for HAQ-DI, 0.4 for the RAQoL, 0.5 for SF-36 PCS and 0.2 for the SF-36 MCS.

Harms

During the experimental period of 52 weeks, no SAEs related to the intervention were reported. The deaths of two patients in

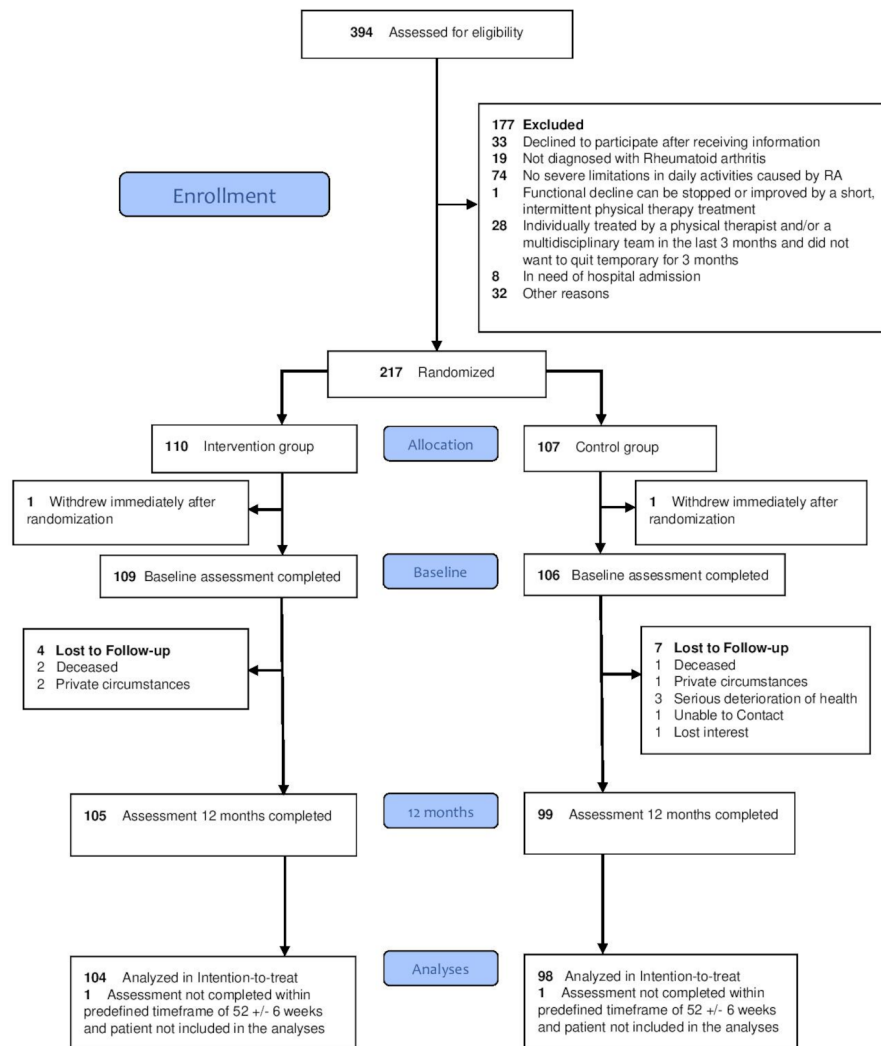


Figure 1 Flow chart. RA, rheumatoid arthritis.

the intervention group had no relation with the exercise therapy treatment (cancer). One AE was recorded in the intervention group, that is, a participant reported dizziness and nausea during aerobic training. The symptoms subsided after 10 min of rest and the treatment was continued.

At 52 weeks, 89 of the 99 participants (90%) in the intervention group who had used the intervention and 45 of the 72 (63%) participants in the usual care group who had used physical therapy (43 conventional physical therapy and 2 erroneously the intervention) completed the questions on the occurrence and severity of muscle soreness and fatigue. The occurrence of muscle soreness related to the intervention or other physical therapy treatment was reported by 70% (n=62 of 89) and 60% (n=27 of 45) and fatigue by 71% (n=63 of 89) and 64% (n=29 of 45) of patients in the intervention and usual care groups, respectively. The average severity of muscle soreness was 3.9 (SD 2.2) and 4.3 (SD 2.6) and of fatigue 4.4 (SD 2.4) and 3.9 (SD 2.9) in patients in the intervention and usual care groups, respectively.

DISCUSSION

This study demonstrates the effectiveness of longstanding (52 weeks), personalised, supervised exercise therapy in people with RA and severe functional limitations compared with usual care. The intervention group showed significantly greater improvements than the usual care group in the primary outcome

(PSC NRS) and various other measures of functional ability and quality of life, with the exception of the SF-36 MCS.

To our knowledge, this is the first study on a longstanding primary care exercise intervention in the specific population of people with RA and severe functional disability. The complexity of their condition was illustrated by the considerable proportions with multiple comorbidities and fulfilling the criteria for D2T RA.^{4,5} Participants in the only previous RCT that included patients with RA with active disease, executed in the rehabilitation setting, had an average baseline HAQ-DI score comparable with our population (ie, 1.8 and 1.7 in the dynamic and conventional exercise groups).¹⁹ Despite the relatively small sample size and short duration of the intervention in that study, a clinically relevant, but statistically non-significant, difference in improvement of the HAQ-DI of -0.2 (95% CI -0.7, 0.3) was seen.¹⁹ Although not statistically significant, its magnitude was in the same range of the treatment effect observed in the present study and may suggest the potential of exercise therapy in patients with RA who are often excluded from clinical trials on exercise therapy.

In our study, according to most secondary endpoints, an effect of the intervention was already seen at 26 weeks. Moreover, about 20% of the patients in the intervention group discontinued treatment before its anticipated duration of 52 weeks. Despite these observations, the design of the study does not

Table 1 Baseline demographics and disease characteristics of participants in a randomised controlled trial on longstanding, personalised exercise therapy

	Intervention group (N=109)	Usual care group (N=106)
Female, N (%)	97 (89.0)	97 (91.5)
Age in years, mean (SD)	59.4 (12.1)	58.1 (13.6)
Age in categories		
18–40 years, N (%)	9 (8.3)	12 (11.3)
41–65 years, N (%)	69 (63.3)	60 (56.6)
≥66 years, N (%)	31 (28.4)	34 (32.1)
BMI (kg/m ²), mean (SD)	27.2 (5.0)	27.9 (6.9)
Single-person household, N (%)	30 (27.5)	37 (34.9)
Higher education§, N (%)	35 (32.1)	27 (25.5)
Work status, N (%)		
≤66 years old, N (%)	82 (75.2)	72 (67.9)
Paid job, N (%)	23 (28.0)	22 (30.6)
No job, health problems, N (%)	32 (39.0)	29 (40.3)
No job, other reasons, N (%)	27 (32.9)	21 (29.2)
Health insurance with additional coverage, N (%)	96 (88.1)	98 (92.5)
≥12 physical therapy treatments, N (%)	84 (87.5)	83 (84.7)
Self-reported duration of complaints (years), mean (SD)	21.6 (12.6)	21.6 (14.0)
Years since diagnosis (years), mean (SD)	18.0 (11.9) (N=102)	19.7 (14.1) (N=91)
Difficult-to-treat RA criteria*, fulfilment, N (%)	44 (43.6) (N=101)	46 (51.1) (N=90)
Rheumatoid factor positive, N (%)	69 (68.3) (N=101)	58 (67.4) (N=86)
ACPA positive, N (%)	58 (60.4) (N=96)	55 (62.5) (N=88)
DAS-28†, mean (SD)	3.0 (1.3) (N=83)	3.2 (1.3) (N=76)
DAS-28 score <2.6 (remission), N (%)	34 (41.0)	27 (35.5)
DAS-28 score 2.6–3.2 (mild), N (%)	14 (16.9)	14 (18.4)
DAS-28 score >3.2–5.1 (moderate), N (%)	30 (36.1)	29 (38.2)
DAS-28 score >5.1 (high), N (%)	5 (6.0)	6 (7.9)
HAQ-DI‡, mean (SD)	1.7 (0.5)	1.7 (0.5)
HAQ-DI score 0–1 (mild), N (%)	12 (11.0)	9 (8.5)
HAQ-DI score >1–2 (moderate-severe), N (%)	74 (67.9)	79 (74.5)
HAQ-DI score >2–3 (severe-very severe), N (%)	23 (21.1)	18 (17.0)
Current medication use, N (%)		
Any DMARD	76 (69.7)	73 (68.9)
bDMARD	56 (73.7)	58 (68.5)
tsDMARD	5 (6.6)	7 (9.6)
csDMARD	51 (67.1)	35 (47.9)
NSAIDs	54 (49.5)	44 (41.5)
Glucocorticoids oral	25 (22.9)	26 (24.5)
Glucocorticoids injection intramuscular/intra-articular	20 (18.3)	11 (10.4)
No RA treatment-related medication	5 (4.6)	5 (4.7)
Smoking status: ever smoked, N (%)	60 (55.0)	68 (64.2)
Number of comorbidities, N (%)	N=108	N=105
0	3 (2.8)	5 (4.8)
1–2	23 (21.3)	28 (26.7)
3–4	39 (36.1)	33 (31.4)
≥5	43 (39.8)	39 (37.1)
Joint replacement surgeries ≥1, N (%)	41 (37.6)	39 (36.8)

Continued

Table 1 Continued

	Intervention group (N=109)	Usual care group (N=106)
*Difficult-to-treat RA definition based on Nagy <i>et al.</i> ⁴⁵		
†The DAS-28 score ²⁷ was based on the ESR and if the DAS-28 score was based on the CRP score, the following calculation was used: DAS-28-ESR=3.3928×Ln (DAS-28-CRP)+0.0254. ⁵⁰ The cut-off points of the DAS-28 score categories were based on Fleischmann <i>et al.</i> ²⁸		
‡Cut-off points of the HAQ-DI were based on Bruce and Fries. ⁴²		
§Higher education=bachelor or master at University (of Applied Sciences).		
ACPA, anti-citrullinated protein antibodies; bDMARD, biological DMARD; BMI, body mass index; CRP, C reactive protein; csDMARD, conventional synthetic DMARD; DAS-28, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; tsDMARD, targeted synthetic DMARD.		

permit conclusions on whether shorter interventions would lead to comparable results. For that purpose, an RCT comparing similar interventions but with different lengths would be needed.

With the interpretation of the effectiveness observed in the present study, the considerable use of physical therapy in the usual care group must be taken into account, as this may have diminished the contrast between the treatment arms. Our findings may thus suggest that the specific elements of the experimental intervention, in particular the focus on individual goals and active exercises, may have played a crucial role in the observed effect. It can however not be ruled out that a similar approach was employed in previous RCTs on exercise therapy in RA, as interventions were in general poorly described, in particular regarding the aspect of personalisation of treatment. Nevertheless, our results are consistent with the literature on the effectiveness of similar exercise interventions in elderly people and people with knee osteoarthritis and complex health problems.^{22–24}

In our study, no effect of the intervention on mental functioning as measured by the SF-36 MCS was seen. Although the intervention was not specifically aimed at addressing psychological well-being, beneficial effects on mental well-being have been demonstrated in other studies on exercise and/or physical activity promotion. However, given the relatively favourable baseline average SF-36 MCS score in our study, there may have been relatively little room for improvement regarding mental health.

With respect to the risk of harms, apart from transient and mild muscle soreness and fatigue reported by the majority of patients, only one AE that was most likely related to the intervention was reported. Therefore, the results suggest that the risk of harms of active exercise therapy, if applied according to the intervention protocol, is very low in patients with RA with complex disease.

Regarding the recruitment of patients, we anticipated challenges to reach out to the specific subgroup. Apart from the impact of the COVID-19 pandemic on the recruitment rate, it appears that, despite all efforts to disseminate information on the trial, it may not have reached all potentially eligible patients and clinicians. This hypothesis is supported by the substantial response to targeted, personalised mailings to patients with RA in two centres. With respect to the latter, the possible role of clinicians' unfamiliarity with the trial, a lack of awareness of functional limitations among their patients with RA or other factors such as time constraints during consultations remain to be established.

Table 2 Differences between groups for the primary outcome (Patient-Specific Complaints activity ranked 1, PSC1 NRS) and secondary outcomes (PSC2 and PSC3 NRS and 6MWT) at 52 weeks: intention-to-treat analyses

	Intervention group			Usual care group			Intervention vs usual care group
	Baseline mean (SD)	52 weeks mean (SD)	Mean change (95% CI)	Baseline mean (SD)	52 weeks mean (SD)	Mean change (95% CI)	Mean difference* in change scores between groups (95% CI)
N	104	104	104	98	98	98	202
Primary outcome							
PSC NRS 1† (0–10)	7.5 (1.4)	4.8 (2.4)	−2.7 (−3.3, −2.2)	7.5 (1.2)	6.5 (2.2)	−1.0 (−1.5, −0.5)	−1.7 (−2.4, −1.0)
Secondary outcome							
PSC NRS 2‡ (0–10)	7.5 (1.3)	4.7 (2.6)	−2.8 (−3.3, −2.3)	7.4 (1.3)	6.4 (2.3)	−1.0 (−1.5, −0.6)	−1.8 (−2.4, −1.1)
PSC NRS 3‡ (0–10)	7.5 (1.4)	4.5 (2.5)	−3.0 (−3.5, −2.6)	7.6 (1.2)	6.3 (2.3)	−1.3 (−1.8, −0.9)	−1.7 (−2.4, −1.0)
6MWT‡ (metres)	311 (92) (n=100)	379 (106) (n=100)	69 (55, 82)	313 (98) (n=89)	325 (110) (n=89)	12 (−1, 26)	56 (38, 75) (n=189)

*Mean difference based on the unpaired Student's t-test.
†Primary outcome measure.
‡Secondary outcome measures.
6MWT, 6-minute walk test; N, number of patients; NRS, Numerical Rating Scale.

Concerning the future implementation of the results of the study, the completion of the trial substantiates the feasibility of recruiting and training primary care PTs to deliver a complex intervention. For a wider, national implementation, a tailored strategy will be developed in collaboration with all relevant stakeholders. It is conceivable that in the future, the intervention will be available to all patients with RA and severe disability, irrespective of current use of physical therapy. When eligible patients who are already using physical therapy change to the intervention, it remains to be established whether the number of intervention treatment sessions they need is lower than the average observed in the intervention group in our trial. On the international level, healthcare services may vary largely. Access to primary care physical therapy may be different across

countries, and depend on factors such as availability of PTs, their level of expertise and the reimbursement of treatment. In some countries, the particular group of patients with RA and severe disability may be admitted to a hospital or rehabilitation centre, whereby a comprehensive treatment in primary care may offer a promising alternative.

Strengths of the study include the randomised design, the large sample size and low drop-out rate. Moreover, the treatment was provided according to a clear protocol, and all PTs providing the intervention were trained. Weaknesses of the study were that patients were aware of the group they were assigned to and the blinded assessors performing the assessments became, despite all efforts for concealment, aware of their randomisation status in some patients or could rightly guess their allocation. The rate of

Table 3 Differences between groups for the secondary outcomes at 26 and 52 weeks: intention-to-treat analyses

Outcome measure	Time points	Intervention group		Usual care group		Estimated mean differences* between groups	
		N	Mean (SD)	N	Mean (SD)	β	95% CI
PROMIS PF-10 (13.5–61.9)	Baseline	107	33.6 (5.4)	104	34.2 (4.9)		
	26 weeks	92	35.7 (5.7)	90	33.9 (5.3)	2.42	(1.37, 3.46)
	52 weeks	100	36.7 (6.2)	91	33.9 (6.0)	3.09	(1.80, 4.38)
HAQ-DI (0–3)†	Baseline	107	1.7 (0.5)	104	1.7 (0.5)		
	26 weeks	92	1.6 (0.5)	90	1.7 (0.5)	−0.11	(−0.20, −0.02)
	52 weeks	100	1.5 (0.6)	91	1.7 (0.5)	−0.17	(−0.29, −0.06)
RAQoL (0–30)†	Baseline	107	16.7 (6.3)	104	15.5 (5.8)		
	26 weeks	92	16.2 (7.2)	90	15.7 (6.1)	−0.75	(−1.84, 0.34)
	52 weeks	98	14.9 (6.6)	91	15.7 (6.4)	−2.03	(−3.38, −0.69)
SF-36 PCS (0–100)	Baseline	107	29.8 (7.6)	104	29.3 (8.2)		
	26 weeks	91	31.9 (8.2)	90	29.1 (8.7)	2.28	(0.28, 4.28)
	52 weeks	98	33.3 (8.9)	91	28.9 (9.6)	3.83	(1.49, 6.17)
SF-36 MCS (0–100)	Baseline	107	46.2 (12.4)	104	47.4 (12.4)		
	26 weeks	91	45.5 (12.4)	90	46.9 (11.6)	−0.31	(−2.90, 2.28)
	52 weeks	98	47.8 (10.9)	91	46.5 (11.4)	2.54	(−0.47, 5.54)

*Mean difference based on linear mixed model.
†Lower score indicates better outcome.
HAQ-DI, Health Assessment Questionnaire-Disability Index; MCS, Mental Component Summary Scale; N, number of patients; PCS, Physical Component Summary Scale; PROMIS PF-10, Patient Reported Outcome Measurement Information System Physical Function-10; RAQoL, Rheumatoid Arthritis Quality of Life; SF-36, 36-Item Short-Form Health Survey.

failure of concealment was in the same range of that in another RCT on exercise in RA, where assessors correctly guessed the allocation in 75% of the patients.⁴⁸ It can thus not be ruled out that awareness of the patient's allocation status had an impact on the measurements, in particular the administration of the PSC and the 6MWT. Moreover, a few patients in the intervention group did not start treatment, whereas as previously mentioned, some patients discontinued treatment before the anticipated duration of at least 1 year. The latter observation may suggest that the intervention was too long for some patients, for example, some reached their treatment targets before ending the first year. In addition, two patients in the usual group received the intervention by mistake and the delivery of regular physical therapy in the usual group was substantial. These situations may have lowered the contrast between study arms, so the observed effect of the intervention may have been underestimated. We did not gather information on medication changes during the 52-week study period, so it is unknown to what extent possible differences between the groups could have affected the results of the trial. Although the promotion of physical activity according to public health recommendations for health-enhancing physical activity^{16,17} was part of the intervention, not only to reduce symptoms but also with the ultimate aim to reduce the cardiovascular risk,⁴⁹ we did not include the amount of physical activity as an outcome measure. It thus remains to be established if the intervention was effective in this respect, and if so, to what extent the physical activity part of the intervention should be combined with other lifestyle interventions such as a healthy diet, weight management or smoking cessation. Moreover, measurements on the level of 'Body Functions and Structures', such as pain, fatigue or muscle weakness, were not included as outcome measures, whereas their systematic monitoring could have been useful to study their potential mediating role.

In conclusion, longstanding, personalised, supervised exercise therapy was more effective with respect to functional ability and quality of life than usual care over 52 weeks of treatment in people with RA and severe functional limitations. Further research is needed to explore the long-term outcomes and potential factors influencing treatment response, as well as the cost-effectiveness of the intervention.

Author affiliations

¹Orthopaedics, Rehabilitation and Physical Therapy, Leiden University Medical Center, Leiden, The Netherlands

²Rheumatology, Sint Maartenskliniek, Nijmegen, The Netherlands

³Center for Rehabilitation and Rheumatology, Reade, Amsterdam, The Netherlands

⁴Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands

⁵Department of Research, Sint Maartenskliniek, Nijmegen, The Netherlands

⁶Rheumatology, Radboudumc, Nijmegen, The Netherlands

⁷Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

Acknowledgements This research would not have been possible without the cooperation of many people. We would like to acknowledge the work of: Mrs S de Jong, Mrs N Lopuhaä and colleagues from the Dutch Arthritis Society for their support with the preparation of the trial and the recruitment of participants; Professor Dr A van Tubergen for all contributions to this study next to the advisory group; all members of the steering group; all physical and exercise therapists who participated in the training and treatment of patients and/or have made their practice available for the assessments; all rheumatologists, nurse specialists, physician assistants and other clinicians who informed patients about the study and/or were involved in active recruitment strategies and/or provided information on participants' characteristics; all medical students who voluntarily supported the research team with the enormous number of administrative tasks (Jitske Hakbijn, Bobbi Straathof, Sjors van de Vusse, Sofie van den Doel, Valentina Petrassi, Marieke Boelhouwers, Wouter Zuidgeest, Cato Smulders, Kjartan Gudmunsson, Immuee Wammes and Tim van der Doef); Mrs I Hoeve for her continuous support in the administration of the reimbursement for the therapists involved; and Dr M de Rooij for her valuable contribution to writing the treatment protocol.

Contributors SFEvW, TPMVV, WFP, AAdB, DvS, WBvdH, CHMVdE and MGJG made substantial contributions to the conception and design of the study. WFP and SFEvW performed the randomisation, recruitment and training of physical therapists and administrative procedures. MMHT and MATvW had a substantial role in the acquisition of data. The analyses and the interpretation of the data were conducted by MMHT, TPMVV, SFEvW, MATvW, CHMVdE and MGJG. All authors were involved in drafting the work or revising it critically for important intellectual content. All authors approved the final version to be published and agreed to be accountable for all aspects of the work. TPMVV is the guarantor, she accepts full responsibility for the work and/or the conduct of the study, had access to the data and controlled the decision to publish.

Funding This project is financially supported by the Netherlands Organization for Health Research and Development (ZonMw; 852004018), Ministry of Health, Welfare and Sport (Ministerie van Volksgezondheid, Welzijn en Sport), the Royal Dutch Society for Physical Therapy (KNGF) and the Dutch Arthritis Society (ReumaNederland).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by by the Medical Ethical Review Board Leiden-Den Haag-Delft (METC-LDD, NL69866.058.19). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs

Max M H Teuwen <http://orcid.org/0000-0002-3235-7800>

Salima F E van Weely <http://orcid.org/0000-0001-8560-4687>

Thea P M Vliet Vlieland <http://orcid.org/0000-0001-6322-3859>

Maria A T van Wissen <http://orcid.org/0000-0002-2998-4256>

Wilfred F Peter <http://orcid.org/0000-0003-1456-2429>

Dirkjan van Schaardenburg <http://orcid.org/0000-0003-4006-3762>

Wilbert B van den Hout <http://orcid.org/0000-0002-6425-0135>

Cornelia H M Van den Ende <http://orcid.org/0000-0002-4352-2824>

Maaike G J Gademan <http://orcid.org/0000-0002-6106-3385>

REFERENCES

- GBD 2021 Rheumatoid Arthritis Collaborators. Global, regional, and national burden of rheumatoid arthritis, 1990–2020, and projections to 2050: a systematic analysis of the global burden of disease study 2021. *Lancet Rheumatol* 2023;5:e594–610.
- Almutairi K, Nossent J, Preen D, et al. The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. *Rheumatol Int* 2021;41:863–77.
- Roodenrijs NMT, de Hair MJH, van der Goes MC, et al. Characteristics of difficult-to-treat rheumatoid arthritis: results of an international survey. *Ann Rheum Dis* 2018;77:1705–9.
- Nagy G, Roodenrijs NMT, Welsing PMJ, et al. EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2022;81:20–33.
- Nagy G, Roodenrijs NM, Welsing PM, et al. EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2021;80:31–5.
- Hsieh P-H, Wu O, Geue C, et al. Economic burden of rheumatoid arthritis: a systematic review of literature in biologic era. *Ann Rheum Dis* 2020;79:771–7.
- Taylor PC, Moore A, Vasilescu R, et al. A structured literature review of the burden of illness and unmet needs in patients with rheumatoid arthritis: a current perspective. *Rheumatol Int* 2016;36:685–95.
- Michaud K, Pope J, van de Laar M, et al. Systematic literature review of residual symptoms and an unmet need in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2021;73:1606–16.
- Heinimann K, von Kempis J, Sauter R, et al. Long-term increase of radiographic damage and disability in patients with RA in relation to disease duration in the era of biologics. *J Clin Med* 2018;7:57.

- 10 Bombardier C, Barbieri M, Parthan A, *et al.* The relationship between joint damage and functional disability in rheumatoid arthritis: a systematic review. *Ann Rheum Dis* 2012;71:836–44.
- 11 Radner H, Smolen JS, Aletaha D. Impact of comorbidity on physical function in patients with rheumatoid arthritis. *Ann Rheum Dis* 2010;69:536–41.
- 12 Combe B, Landewe R, Daien CI, *et al.* Update of the EULAR recommendations for the management of early arthritis. *Ann Rheum Dis* 2017;76:948–59.
- 13 National Institute for Health and Care Excellence (NICE). Rheumatoid arthritis in adults: management [nice.org.uk]. Available: [rheumatoid-arthritis-in-adults-management-pdf-66141531233989](https://www.nice.org.uk/guidance/CG142) [Accessed 27 Oct 2023].
- 14 England BR, Smith BJ, Baker NA, *et al.* American college of rheumatology guideline for exercise, rehabilitation, diet, and additional integrative interventions for rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2023;75:1603–15.
- 15 Gwinnutt JM, Wiecek M, Rodríguez-Carrio J, *et al.* Effects of physical exercise and body weight on disease-specific outcomes of people with rheumatic and musculoskeletal diseases (RMDs): systematic reviews and meta-analyses informing the 2021 EULAR recommendations for lifestyle improvements in people with RMDs. *RMD Open* 2022;8:e002167.
- 16 Rausch Osthoff A-K, Juhl CB, Knittle K, *et al.* Effects of exercise and physical activity promotion: meta-analysis informing the 2018 EULAR recommendations for physical activity in people with rheumatoid arthritis, spondyloarthritis and hip/knee osteoarthritis. *RMD Open* 2018;4:e000713.
- 17 Rausch Osthoff A-K, Niedermann K, Braun J, *et al.* EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. *Ann Rheum Dis* 2018;77:1251–60.
- 18 Ye H, Weng H, Xu Y, *et al.* Effectiveness and safety of aerobic exercise for rheumatoid arthritis: a systematic review and meta-analysis of randomized controlled trials. *BMC Sports Sci Med Rehabil* 2022;14:17.
- 19 van den Ende CH, Breedveld FC, le Cessie S, *et al.* Effect of intensive exercise on patients with active rheumatoid arthritis: a randomised clinical trial. *Ann Rheum Dis* 2000;59:615–21.
- 20 Edelaar L, Nikiphorou E, Fragoulis GE, *et al.* EULAR recommendations for the generic core competences of health professionals in rheumatology. *Ann Rheum Dis* 2020;79:53–60.
- 21 Peter WF, Swart NM, Meerhoff GA, *et al.* Clinical practice guideline for physical therapist management of people with rheumatoid arthritis. *Phys Ther* 2021;101:pzab127.
- 22 de Vries NM, van Ravensberg CD, Hobbelen JSM, *et al.* The Coach2Move approach: development and acceptability of an individually tailored physical therapy strategy to increase activity levels in older adults with mobility problems. *J Geriatr Phys Ther* 2015;38:169–82.
- 23 de Vries NM, Staal JB, van der Wees PJ, *et al.* Patient-centred physical therapy is (Cost-) effective in increasing physical activity and reducing frailty in older adults with mobility problems: a randomized controlled trial with 6 months follow-up. *J Cachexia Sarcopenia Muscle* 2016;7:422–35.
- 24 de Rooij M, van der Leeden M, Cheung J, *et al.* Efficacy of tailored exercise therapy on physical functioning in patients with knee osteoarthritis and comorbidity: a randomized controlled trial. *Arthritis Care Res (Hoboken)* 2017;69:807–16.
- 25 van Wissen MAT, Teuwen MMH, van den Ende CHM, *et al.* Effectiveness and cost-effectiveness of longstanding exercise therapy versus usual care in patients with axial spondyloarthritis or rheumatoid arthritis and severe limitations: the protocols of two parallel randomized controlled trials. *Physiother Res Int* 2022;27:e1933.
- 26 Staniszewska S, Brett J, Simeria I, *et al.* GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. *Res Involv Engagem* 2017;3:13.
- 27 Prevoo ML, van 't Hof MA, Kuper HH, *et al.* Modified disease activity scores that include twenty-eight-joint counts. development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44–8.
- 28 Fleischmann RM, van der Heijde D, Gardiner PV, *et al.* DAS28-CRP and DAS28-ESR cut-offs for high disease activity in rheumatoid arthritis are not interchangeable. *RMD Open* 2017;3:e000382.
- 29 Hoffmann TC, Glasziou PP, Boutron I, *et al.* Better reporting of interventions: template for intervention description and replication (TIDier) checklist and guide. *BMJ* 2014;348:g1687.
- 30 World Health Organisation (WHO). International classification of disability, functioning and health: ICF. Geneva WHO; 2001. Available: <https://www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health> [Accessed 21 Oct 2023].
- 31 Schenkman M, Deutsch JE, Gill-Body KM. An integrated framework for decision making in neurologic physical therapist practice. *Phys Ther* 2006;86:1681–702.
- 32 Rothstein JM, Echenach JL, Riddle DL. The hypothesis-oriented algorithm for Clinicians II (HOAC II): a guide for patient management. *Phys Ther* 2003;83:455–70.
- 33 Meyer T, Weiss C, Rathore FA. Goal setting in medical rehabilitation: a narrative review. *J Pak Med Assoc* 2023;73:1923–5.
- 34 Hoogeboom TJ, Kousemaker MC, van Meeteren NL, *et al.* I-CONTENT tool for assessing therapeutic quality of exercise programs employed in randomised clinical trials. *Br J Sports Med* 2021;55:1153–60.
- 35 Garber CE, Blissmer B, Deschenes MR, *et al.* American college of sports medicine position stand. quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011;43:1334–59.
- 36 Beurskens AJ, de Vet HC, Köke AJ, *et al.* A patient-specific approach for measuring functional status in low back pain. *J Manipulative Physiol Ther* 1999;22:144–8.
- 37 Stevens A, Köke A, van der Weijden T, *et al.* Ready for goal setting? Process evaluation of a patient-specific goal-setting method in physiotherapy. *BMC Health Serv Res* 2017;17:618.
- 38 Gershon RC, Rothrock N, Hanrahan R, *et al.* The use of PROMIS and assessment center to deliver patient-reported outcome measures in clinical research. *J Appl Meas* 2010;11:304–14.
- 39 Terwee CB, Roorda LD, de Vet HCW, *et al.* Dutch-Flemish translation of 17 item banks from the patient-reported outcomes measurement information system (PROMIS). *Qual Life Res* 2014;23:1733–41.
- 40 Boers M, Jacobs JWG, van Vliet Vlieland TPM, *et al.* Consensus Dutch health assessment questionnaire. *Ann Rheum Dis* 2007;66:132–3.
- 41 Fries JF, Spitz P, Kraines RG, *et al.* Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137–45.
- 42 Bruce B, Fries JF. The Stanford health assessment questionnaire: dimensions and practical applications. *Health Qual Life Outcomes* 2003;1:20.
- 43 Whalley D, McKenna SP, de Jong Z, *et al.* Quality of life in rheumatoid arthritis. *Br J Rheumatol* 1997;36:884–8.
- 44 Aaronson NK, Muller M, Cohen PD, *et al.* Translation, validation, and Norming of the Dutch language version of the SF-36 health survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055–68.
- 45 Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. *Medical Care* 1992;30:473–83.
- 46 Butland RJ, Pang J, Gross ER, *et al.* Two-, six-, and 12-minute walking tests in respiratory disease. *Br Med J (Clin Res Ed)* 1982;284:1607–8.
- 47 Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003;41:582–92.
- 48 de Jong Z, Munneke M, Zwinderman AH, *et al.* Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. *Arthritis Rheum* 2003;48:2415–24.
- 49 Metsios GS, Moe RH, van der Esch M, *et al.* The effects of exercise on cardiovascular disease risk factors and cardiovascular physiology in rheumatoid arthritis. *Rheumatol Int* 2020;40:347–57.
- 50 Leong KP, Tan JWL, Gao X, *et al.* Conversion among the 28-joint count activity indices for rheumatoid arthritis. *Eur J Rheumatol* 2020;7:105–11.