Exercise therapy in people with rheumatoid arthritis and severe functional disability

Max M.H. Teuwen

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Chapter 1

General introduction

Epidemiology and pathophysiology of RA

Rheumatoid arthritis (RA) is a chronic autoimmune disease primarily characterized by inflammation, pain, stiffness and swelling of the peripheral joints [1, 2]. It affects approximately 0.5% of the population worldwide and most commonly starts between the ages of 30 and 60 years. RA is more common in women than in men [3]. The exact cause of RA remains unknown, however a combination of genetic and environmental factors is found to contribute to its development [1, 2]. The inflammatory process of RA is thought to start with the accumulation of autoreactive T cells and B cells in the synovial tissues, which are the primary target sites of inflammation in the joints [4, 5]. Activated T cells can stimulate B cells to produce autoantibodies, particularly rheumatoid factors and anti-citrullinated protein antibodies (ACPA) [4, 5]. When the inflammation becomes chronic this leads to the distinctive joint symptoms of RA, and progressive joint destruction if left untreated [4, 5] (Fig. 1).

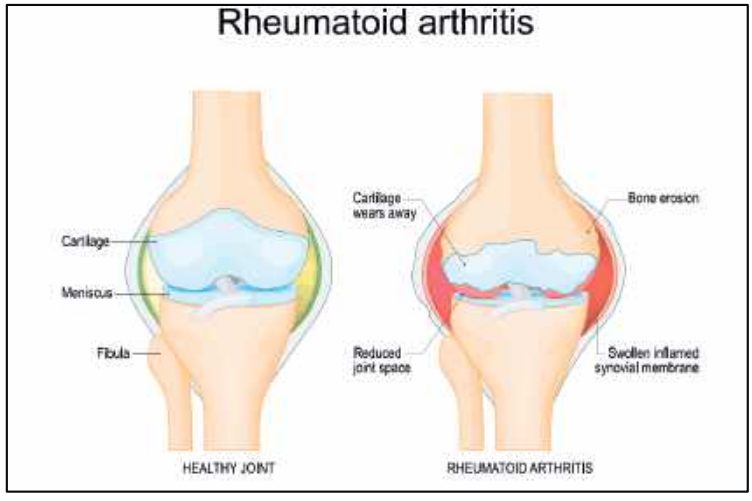

Figure 1 A healthy knee joint versus a knee joint exhibiting symptom of RA.

Beyond the characteristic joint symptoms linked to RA, the systemic nature of this autoimmune disorder can also lead to general symptoms such as fatigue and specific extra-articular manifestations such as episcleritis, anemia, chronic leg ulcers, vasculitis, pleural effusion, osteoporosis, peripheral neuropathy, hematological malignancies and Sjogren's syndrome [6]. Moreover, people with RA have an increased risk of developing cardiovascular disease [7]. The latter is related to the chronic inflammation, which may

contribute to arterial plaque formation, potentially leading to hypertension, heart attacks, and other cardiovascular complications [7]. Patients diagnosed with RA face a significantly elevated mortality risk compared to the general population [8]. Cardiovascular diseases stand out as the predominant cause of death in RA patients. Furthermore, other common causes of death in RA patients are infections, pulmonary complications, and renal diseases [8].

Clinical impact of RA

Impact of RA described through the ICF

The impact of RA on the individual may be substantial. Symptoms including joint pain, swelling and limited range of motion and fatigue affect the lives of people with RA and their families in multiple areas. The consequences of RA can be comprehensively described according to the World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF) [9]. The ICF is a comprehensive framework for the description of health and health-related domains. These domains are classified by means of two lists: a list of body functions and structures, and a list of domains of activities and participation [10]. In the ICF, the term functioning refers to all body functions, activities and participation, while disability is similarly an umbrella term for impairments, activity limitations and participation restrictions [10]. In the ICF, functioning and disability are viewed as outcomes of interactions between health conditions (diseases, disorders and injuries) and contextual factors. Contextual factors are external environmental factors (e.g., social attitudes, architectural characteristics, or social and health care structures); and internal personal factors e.g., gender, age, coping styles, social background, education, character and other factors that influence how disability is experienced by the individual [10]. Regarding the health domains that are most relevant for people with RA specifically, so called ICF Core Sets for RA have been developed [11]. ICF Core Sets for RA identify essential health categories for precise descriptions of functioning in clinical settings. ICF Core Sets for RA include the Comprehensive and Brief version. The Comprehensive Core Set is primarily designed for interdisciplinary assessments by providing an extensive set of categories. In contrast, the Brief Core Set contains fewer categories and is primarily tailored for clinical studies and encounters within a single profession. An overview of the ICF categories from the Brief Core Set for RA are displayed in Table 1.

Table 1 International Classification of Functioning, Disability and health (ICF): categories of the components body functions, body structures, activities and participation and environmental factor included in the ICF Brief Core Set for RA [11].

Body functions (b), n=5	Body structures (s), n=4	Activities and participation (d), n=6	Environmental factors (e), n=5
b280 Sensation of pain	s710 Structure of head and neck region	d230 Carrying out daily routine	e115 Products and technology for personal use in daily living
b455 Exercise tolerance functions	s720 Structure of shoulder region	d410 Changing basic body position	e310 Immediate family
b710 Mobility of joint functions	s730 Structure of upper extremity	d440 Fine hand use	e355 Health professionals
b730 Muscle power functions	s750 Structure of lower extremity	d445 Hand and arm use	e570 Social security services, systems and policies
b780 Sensations related to muscles and		d450 Walking	e580 Health services, systems and policies
		d850 Remunerative employment	

Functional disability in RA

Functional disability is prevalent among RA patients, commonly assessed through metrics like the Health Assessment Questionnaire Disability Index (HAQ-DI) or by evaluating difficulties in performing activities of daily living. A number of studies have shown that in RA the prevalence of functional disability (functional limitations progressing to the loss of independence in activities of daily living) is exceeded by 15% as compared to people without RA across various age groups [12, 13]. The connection between functional disability and disease activity in RA has been well-established [14-16]. Despite significant advancements in the medical treatment of RA, a significant proportion of patients, ranging from 5-20%, continues to face challenges in achieving adequate control of disease activity [17-19]. Recently, this condition has been defined as Difficult-to-Treat (D2T) RA [20, 21]. These D2T criteria incorporate the patient's perception that the consequences are problematic, which may include functional disability, but the criteria are overall focused on persisting disease activity. However, also in the absence of significant disease activity, the consequences in terms of functional disability may be substantial, e.g. due to joint damage, deformities, complications from the disease or its treatment, and/or comorbidities [17-19]. In the Netherlands it is estimated that 5% of the people with RA have severe functional disability, defined as RA patients with one or more severe limitations in daily activities and functioning, related to their rheumatic condition, such as: a limited walking distance indoors and/or outdoors, problems with making transfers (bed, chair, using the toilet), incapable of independent self-care (dressing, washing) [22].

Management of RA

The clinical management of RA consists of both pharmacological and non-pharmacological treatment. Over recent decades, there have been notable advancements in medication options, where in particular the biologic disease-modifying anti rheumatic drugs (bDMARDs), and targeted synthetic (ts)DMARDs have improved the outcomes for people with RA dramatically [23, 24]. Nevertheless, many patients have in their disease course periods where symptoms are hampering their daily functioning and societal participation. Therefore, many patients are, apart from medical treatment, in need of non-pharmacological approaches, including expert advice, guidance and/or specific treatments. Additional care is needed not only to support patients in coping with the consequences of the disease, but also to advise them on measures to prevent functional deterioration or comorbidities associated with RA, in particular the adoption of a healthy lifestyle [25, 26].

Regarding the provision of non-pharmacological care, the WHO has recently developed "Packages of interventions for rehabilitation" [27]. These include the most essential interventions for rehabilitation for health conditions that have high prevalence and high levels of associated disability across seven disease areas. One of these packages pertains to RA and includes a description of functional interventions and interventions for the prevention and treatment of secondary conditions related to RA [27]. The functional interventions include cognitive functions, pain management, motor functions, mobility, exercise and fitness, activities of daily living, education and vocation, lifestyle modification, and self-management [27]. Concurrently, interventions aimed at preventing and treating secondary conditions focus on mental health aspects such as depression, anxiety, and emotional distress, as well as addressing concerns related to malnutrition [27]. Given the broad range of non-pharmacological treatment modalities, most professional guidelines for the management of RA recommend a multidisciplinary approach, with apart from the rheumatologist, involvement of other healthcare professionals, including the nurse, clinical nurse specialist or nurse practitioner, physical therapist, occupational therapist, psychologist, social worker, podiatrist, dietician, prosthetists and orthotists or others [21, 28-31].

Exercise therapy in RA – current delivery and effectiveness

Current delivery

In order to support patients in effectively managing and improving or maintaining their health, exercise therapy is an essential aspect of the non-pharmacological management of RA. Physical therapists[1] advise and guide people with RA regarding the most suitable exercises to improve or maintain an optimal level of daily functioning and the adoption of an active lifestyle. For the interpretation of the current state of knowledge on physical therapy and exercise therapy and the promotion of physical activity, it is important to clarify the terminology. Physical activity is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" [32]. Exercise pertains to a subcategory of physical activity, and is defined as: "Planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness" [32]. Exercise therapy involves engaging in functional movements and undertaking aerobic, mobility, strength, and/or neuromotor exercises to enhance physical functioning and participation [33, 34]. Exercise therapy can be administered either individually or in a group setting, facilitated by a physical therapist or other professional, depending on the country [34]. Most exercise therapy programs include a combination of supervised exercises, unsupervised exercises, education, and general physical activity promotion.

Currently, recommendations for the provision of exercise therapy are included in various multidisciplinary guidelines for the management of RA, as highlighted by a systematic review [35], however usually with little information on the precise content, dosage or mode of delivery [35]. In 2021, in the Netherlands, a guideline specifically for physical therapists entitled "Clinical Practice Guideline for Physical Therapist Management of People With Rheumatoid Arthritis" was published [33]. It advises on the desired comprehensive assessment, specific exercises and a personalized exercise plan, and education on self-management strategies, as well as regular assessments and evaluation of the progression. The comprehensive assessment includes a thorough evaluation of the patient's health and the disease impact on daily life according to the ICF. It advises on the desired comprehensive assessment, specific exercises and a personalized exercise plan, and education on self-management strategies, as well as regular assessments and evaluation of

[1] If the term "physical therapist" is used in this thesis, it encompasses both the physical therapist and the exercise therapist/Mensendieck or Cesar therapist, the latter two being relevant professionals delivering exercise therapy in The Netherlands.

the progression. The comprehensive assessment includes a thorough evaluation of the patient's health and the disease impact on daily life according to the ICF. Its results allow categorization into three treatment profiles [33]: Treatment profile 1: Education and exercise instructions with limited supervision; Treatment profile 2: Education and short-term supervised exercise therapy; Treatment profile 3: Education and longstanding supervised exercise therapy due to the presence of serious comorbidity or complications of the disease or its treatment. The management of people with RA and severe functional disability is related to treatment profile 3, where the complexities of their condition requires careful customization and personalization of longstanding exercise therapy plans.

It is estimated that approximately 25-50% of patients with RA visit the physical therapist over a period of 12 months [36-38]. In the Netherlands, treatment is provided by primary care physical therapists in most cases. Access to physical therapy is either by referral by a physician or self-referral (direct access). Physical therapy is not in the national, compulsory basic insurance, and reimbursement depends on whether patients have an additional insurance and if so, its specific coverage.

Evidence for Effectiveness of Exercise Therapy

Several systematic reviews have concluded that exercise therapy is effective in people with RA, reporting various benefits, including improvement of aerobic capacity, muscle strength, functional ability, and reducing pain [39-44]. The available evidence for exercise therapy in RA however primarily relies on randomized controlled trials (RCTs) that have typically focused on specific groups of people with RA, such as those with stable disease, no significant comorbidities, and no weight-bearing joint replacements. One RCT included individuals with active RA requiring multidisciplinary rehabilitation, showing benefits from exercise therapy with an average duration of 30 days [45]. While the ability to personalize treatments is a fundamental skill of health professionals in rheumatology including physical therapists [46], as emphasized in both the Dutch physical therapy guideline for RA management and a recent systematic review outlining core recommendations for RA care [34, 35], addressing the intricacies of treatment in challenging cases may necessitate a specific and targeted approach. Such an approach was such as elderly individuals with mobility issues [47, 48] and those with knee osteoarthritis and multimorbidity [49], the application of these approaches to patients with RA and severe functional disability remains unestablished.

In summary, exercise therapy is generally considered effective in people with RA, but research so far predominantly focused on RA patients with a generally favorable health status, leaving those with severe functional disability due to complex health problems underrepresented. Thus, there is a knowledge gap regarding its value in patients with severe functional disability. These patients are expected to constitute 5% of the RA population and are likely to be in need of longstanding supervised exercise therapy.

Exercise therapy in RA – cost-effectiveness

Besides the evaluation of the effectiveness of exercise therapy interventions, it is important to evaluate their cost-effectiveness as well. The scarcity of healthcare resources necessitates informed decision-making with multiple competing demands. Incorporating economic criteria can guide these decisions, addressing whether the extra health gains are justified by the additional levels of healthcare resources required. In the context of exercise therapy in RA, the number of available economic analyses is limited. This is also emphasized in the umbrella review of systematic reviews on the effectiveness of exercise therapy in rheumatoid arthritis by Hu et al. [39]. The existing economic studies pertained to specific exercise interventions, including a hand exercise program for RA [50] a coaching intervention for physical activity rather than an exercise therapy program [51], or only upper limb exercises [52]. In addition, ambulatory care physical therapy was compared to home-based physical therapy, making it impossible to make a comparison with usual care or no intervention [53]. One economic analysis was done alongside an RCT on a 104-week high-intensity group exercise program in RA, showing increased costs compared to usual care [54]. In that study, which was published more than 20 years ago, it was found that the total medical costs of the longstanding physical therapy intervention were €430 higher than of usual care and the total societal costs were €602 higher [54]. One-year quality adjusted life years (QALYs) were used to guide healthcare resource allocation by measuring the area under utility curves during the follow-up period. With a societal willingness-to-pay of €50,000 per QALY, usual care proved more cost-effective than group exercise. It was thus concluded that from a societal perspective, long-term, high-intensity group exercise lacked substantial health valuation improvements to justify the additional costs [54]. However, it is worth noting that this study was conducted in RA patients with stable disease, having no joint arthroplasties in weight-bearing joints, and with no significant comorbidities.

In conclusion, evaluating the cost-effectiveness of exercise therapy is crucial given limited healthcare resources, however economic analyses of exercise therapy in RA are scarce. In the case of RA patients with severe functional disability, apart from an evaluation of effectiveness, a comprehensive economic analysis is also currently lacking.

Outcome measures in clinical trials on exercise therapy in RA

Functional outcomes: daily activities

In order to demonstrate the value of exercise therapy in RA the use of appropriate outcome measures in clinical trials is vital. These measures include, depending on the outcome on various assessment tools such as performance tests and patient-reported outcomes, but could consist of laboratory tests or imaging as well [55, 56].

Regarding the frequency of the use of various outcome measures in exercise trials in RA, trials predominantly utilized outcome measures related to body structures and functions, and activities of daily living. This is illustrated by the results of a systematic review published in 2022, assessing the efficacy of exercise therapy in RA patients, including a comprehensive analysis of 13 studies [44]. Examples of commonly utilized measures included the assessment of disease activity (for example Disease Activity Score-28 [57]), muscle strength (such as grip strength and isokinetic/dynamic strength) and aerobic capacity (measured by maximal oxygen consumption). Furthermore, the frequent assessment of daily activities in these trials employed a dual approach: Firstly, patient-reported outcome measures, such as the HAQ-DI and second, performance-based measures such as the timed up-and-go test. Measures of participation are addressed least frequently (3 of 13 studies). Measuring functional disability in terms of limitations in daily activities in RA poses particular challenges as the disease is characterized by its heterogeneity, with patients experiencing diverse patterns and degrees of joint involvement, making it difficult to establish a uniform metric for evaluating physical function.

Outcome measures like the Canadian Occupational Performance Measure (COPM) [58], McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR) [59], and the Patient Specific Complaints Instrument (PSC) [60] employ methods of prioritization and elicitation of those activities that are most relevant for individual patients. These measures yield information on the nature and severity of disability on the individual

patient level rather than a general score alone. As such these instruments may be helpful in the process of individual goal setting for rehabilitative interventions including exercise therapy. Considering the limited understanding of the nature of functional disability, conducting an analysis focusing on the description of functional disability using prioritization and elicitation, using the ICF as a reference, could provide new insight in identifying individual functional disability and thus improving treatment.

The HAQ-DI [61] is the most commonly used disease specific measure for functional disability in RA, evaluating the level of difficulty with the execution of 20 specific activities across eight different domains of disability, and the use of help of assistive devices. It yields an overall score ranging from 0 to 3 (0-≤1 (mild), >1-≤2 (moderate-severe), >2-≤3 (severe-very severe)) [62]. It has been applied and validated in patients with a wide variety of rheumatic diseases, including RA [61] and is sensitive to change over time [63]. The literature lacks specific information on the functional disability, particularly within the RA population with severe functional disability. For this subgroup potentially requiring unique support, the absence of an exploration raises crucial questions about their challenges and well-being. Analyzing functional disability using the HAQ-DI and exploring associations can refine healthcare strategies.

A more recent measure is the generic Patient-Reported Outcome Measure Information System Physical Functioning 10-item questionnaire (PROMIS PF-10) [64]. PROMIS measures, using item-response theory, include questionnaires (Item Banks, Short Forms, or Computer Adaptive Tests) for specific and general health domains and they employ a standardized T-score metric centered around the general population, improving interpretability, precision, and comparability of scores across studies and diseases. However, it is important to note that the PROMIS PF-10 is not a disease specific questionnaire like the HAQ-DI. Notably, neither the PROMIS PF-10 nor the HAQ-DI involves the elicitation and prioritization of individual functional problems. So far, experience with this instrument in rheumatology research, including exercise trials, seems limited and an overview of the actual usage of the PROMIS-PF10 is lacking.

Harms outcomes

Furthermore, it is essential to acknowledge that negative outcomes or undesired effects, known as harms can also emerge as a consequence of treatment. Although these are to a certain extent inevitable, it is vital that the side effects do not counteract the beneficial effects. Unfortunately, the systematic approach to capturing harm outcomes is often neglected in studies that investigate exercise therapy [65-68].

In the context of exercise therapy, potential harms encompass issues like muscle pain, exertion, an increase in local or general disease activity, joint damage, or exercise-related injuries such as muscle sprains. For the outcomes of pain and disease activity it is not always clear whether the outcome was intended to measure a positive effect or a negative effect. Prespecifying harm outcomes holds significant importance as it enables researchers to systematically evaluate and document any harms that might arise from the intervention [69-72].

In recent years this topic has gained interest with a number of reviews [65-68] investigating the effects of exercise therapy in several musculoskeletal and rheumatic diseases and addressed harms in trials on the effectiveness of exercise therapy. One particular review concluded on a small risk for non-serious adverse events (AEs) of people with several musculoskeletal complaints participating in exercise programs [66]. In contrast, other reviews did not observe an increased risk of AEs associated with exercise [65, 67, 68]. All the reviews derived their conclusions from a relatively small percentage of included RCTs that provided information on harms as the majority of the trials did not systematically report on harms. Additionally, none of the reviews considered the quality of reporting in their assessments, which has resulted in a lack of comprehensive insight into the nature and risk of harms in trials evaluating the effectiveness of exercise in rheumatic diseases. Enhancing our understanding of the specific harms and benefits can not only improve the reporting but also inform the design and execution of exercise therapy trials within this field and improve the safety for patients.

Aims of this thesis

Taking into account the abovementioned knowledge gaps, particularly in the context of people with RA with severe functional disability, this thesis aims to:

1. Investigate the effectiveness and cost-effectiveness of longstanding supervised exercise therapy in people with RA and severe functional disability (Part I).
2. Explore the usage and applicability of various outcome measures for functional ability of people with RA and of measures for the safety of exercise therapy in this patient group (Part II).

These aims are addressed in the following chapters:

Part I

- **Chapter 2**: Describes the study protocol of the L-EXTRA study on the Effectiveness and cost-effectiveness of longstanding exercise therapy versus usual care in patients with RA and severe limitations.
- **Chapter 3**: Includes a randomized controlled trial which compares the effectiveness of longstanding exercise therapy with usual care for people with RA and severe functional limitations.
- **Chapter 4**: Describes a cost-utility analysis of longstanding exercise therapy versus usual care in people with RA and severe functional limitations.

Part II

- **Chapter 5**: Outlines a study on the nature and functional limitations of people with RA or axial spondyloarthritis (axSpA) and severe functional disability by using the ICF model as a reference.
- **Chapter 6**: Includes an analysis on the extent and nature of functional limitations according to the Health Assessment Questionnaire Disability Index in patients with RA and severe functional disability.
- **Chapter 7**: Describes a systematic review on the use of PROMIS outcomes in clinical studies in patients with inflammatory arthritis.
- **Chapter 8**: Outlines a systematic review on the quality of reporting and nature of harms in clinical trials on supervised exercise in patients with RA or axSpA.
- **Chapter 9**: Provides a comprehensive discussion and summary of the findings of this thesis.

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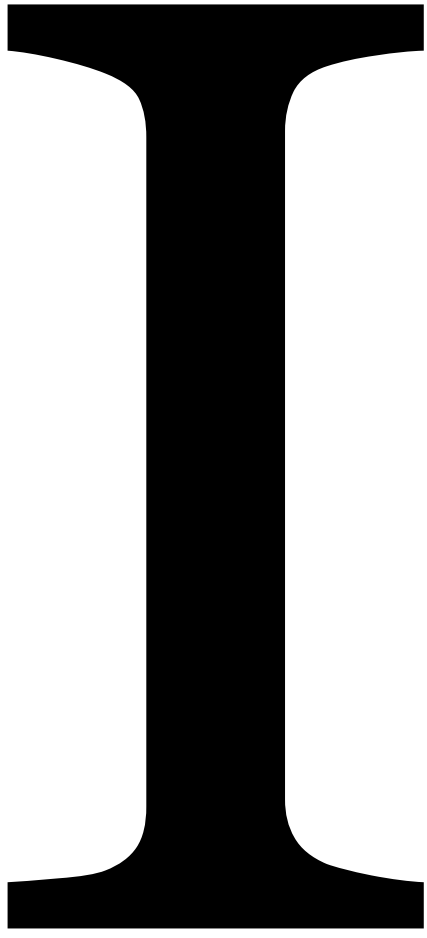

Part I

Effectiveness and Cost-effectiveness of longstanding supervised exercise therapy in people with rheumatoid arthritis

2

Chapter 2

Effectiveness and cost-effectiveness of long-standing exercise therapy versus usual care in patients with axial spondyloarthritis or rheumatoid arthritis and severe limitations: the protocols of two parallel randomized controlled trials

Maria A.T. van Wissen[1] / **Max M.H. Teuwen**[1], Cornelia H. M. van den Ende[2,3], Thea P.M. Vliet Vlieland[1], Alfons A. den Broeder[2,3], Wilbert B. van den Hout[4], Wilfred F. Peter[1], Dirkjan van Schaardenburg[5], Astrid M. van Tubergen[6,7], Maaike G.J. Gademan[1,8], Salima F.E. van Weely[1]

1. Department of Orthopaedics, Rehabilitation and Physical Therapy, Leiden University Medical Center, Leiden, The Netherlands;
2. Department of Rheumatology, Sint Maartenskliniek, Nijmegen, The Netherlands;
3. Department of Rheumatology, Radboud UMC, Nijmegen, The Netherlands;
4. Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands;
5. Center for Rehabilitation and Rheumatology, Reade, Amsterdam, The Netherlands;
6. Department of Rheumatology, Maastricht University Medical Center, Maastricht, The Netherlands;
7. The Netherlands and Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands;
8. Department of Clinical epidemiology, Leiden University Medical Center, Leiden, The Netherlands.

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Abstract

Objectives: Research on effectiveness and cost-effectiveness of longstanding exercise therapy in patients with axial SpondyloArthritis (axSpA) or Rheumatoid Arthritis (RA) is scarce, and mainly concerned patients with a relatively favorable health status. We aim to evaluate the effectiveness and cost-effectiveness of longstanding exercise therapy compared to usual care in the subgroup of patients with axSpA or RA and severe limitations in functioning.

Methods: In two separate, parallel randomized controlled trials the effectiveness and cost-effectiveness of longstanding, active exercise therapy (52 weeks) compared with usual care (1:1) will be evaluated. The longstanding, active exercise therapy will focus on improving individual limitations in daily activities and participation and will be given by a trained physical therapist in the vicinity of the participant. For each diagnosis, 215 patients with severe limitations in activities and participation will be included. Assessments are performed at baseline, 12, 26, and 52 weeks. The primary outcome measure of effectiveness is the individual level of functioning (activities and participation), as measured with the Patient-Specific Complaints instrument at 52 weeks. For cost-effectiveness analyses, the EuroQol (EQ-5D-5L) and questionnaires on healthcare use and productivity will be administered. The economic evaluation will be a cost-utility analysis from a societal perspective. After 52 weeks, the patients in the usual care group are offered longstanding, active exercise therapy as well. Follow-up assessments are done at 104, 156 and 208 weeks.

Conclusion: The results of these studies will provide insights in the effectiveness and cost-effectiveness of longstanding exercise therapy in the subgroup of axSpA and RA patients with severe functional limitations.

Keywords: Axial spondyloarthritis; Exercise therapy; Physical therapy; Randomized controlled trial; Rheumatoid arthritis.

Introduction

Axial SpondyloArthritis (axSpA) and Rheumatoid Arthritis (RA) are chronic rheumatic diseases often with an progressive course, defined by chronic inflammation of the joints, tendons and synovial joint lining [1, 2]. AxSpA is mainly characterized by inflammation of the spine and sacroiliac joints and ankylosis of the spine, and RA by arthritis of the peripheral joints [1, 2]. Joint pain, stiffness and fatigue are major and common symptoms in both diseases, whereas extra-articular manifestations in for example skin, blood vessels or inner organs occur less frequently [3, 4].

The prevalence of ankylosing spondylitis (major subtype of axSpA) varies worldwide from < 0.01% to 1.8% [5], whereas RA affects about 1%-1.5% of the Western population [2, 6]. AxSpA, occurs equally in men and women, whereas RA is more frequent in women. Treatment of both diseases is primarily pharmacological, consisting of non-steroidal anti-inflammatory drugs, conventional biologicals or targeted synthetic disease modifying anti rheumatic drugs and/or glucocorticosteroids [7-9]. In addition, non-pharmacological treatment is given in the majority of patients, of which patient education and exercise therapy constitute the cornerstones.

With respect to exercise therapy in axSpA, multiple systematic reviews concluded that supervised exercise therapy is an effective and safe treatment option, resulting in small to modest improvements in pain, disease activity, functional ability and axial mobility [10-14]. In RA, systematic reviews concluded a moderate, positive effect on aerobic capacity, muscle strength and overall functional ability [15-18].

In general, most of the studies included in these reviews concerned programs of a relatively short duration (≤12 weeks) and mostly concerned patients with stable disease, no co-morbid conditions and relatively favorable functional ability [16, 19, 20]. Patients with active disease, irreversible joint damage, multiple joint replacements and/or severe comorbidity hampering participation in exercise therapy programs are underrepresented in research so far.

Only one trial in RA patients specifically included patients with active disease. Yet that study concerned a short-term program, whereas it is conceivable that patients with severe limitations in activities and participation, due to persistent high disease activity, joint

damage or complications of the disease and/or comorbidity are in need of long-term treatment [21] Consequently, cost-effectiveness studies on physical therapy are also lacking in these specific subgroups. Economic analyses are rare at all in studies on effectiveness on supervised exercise therapy in rheumatic and musculoskeletal diseases [19, 20].

Thus, there is a lack of knowledge on the effect of long-term exercise therapy in the subgroup of patients with severe functional disability. We aim to evaluate the effectiveness and cost-effectiveness of longstanding exercise therapy compared to usual care in the subgroup of patients with axSpA or RA and severe limitations in functioning. We hypothesize that longstanding exercise therapy, tailored to individual patients' needs and optimized according to the latest scientific insights, in the defined subgroups of patients with axSpA or RA and severe functional limitations is effective and cost-effective compared to usual care.

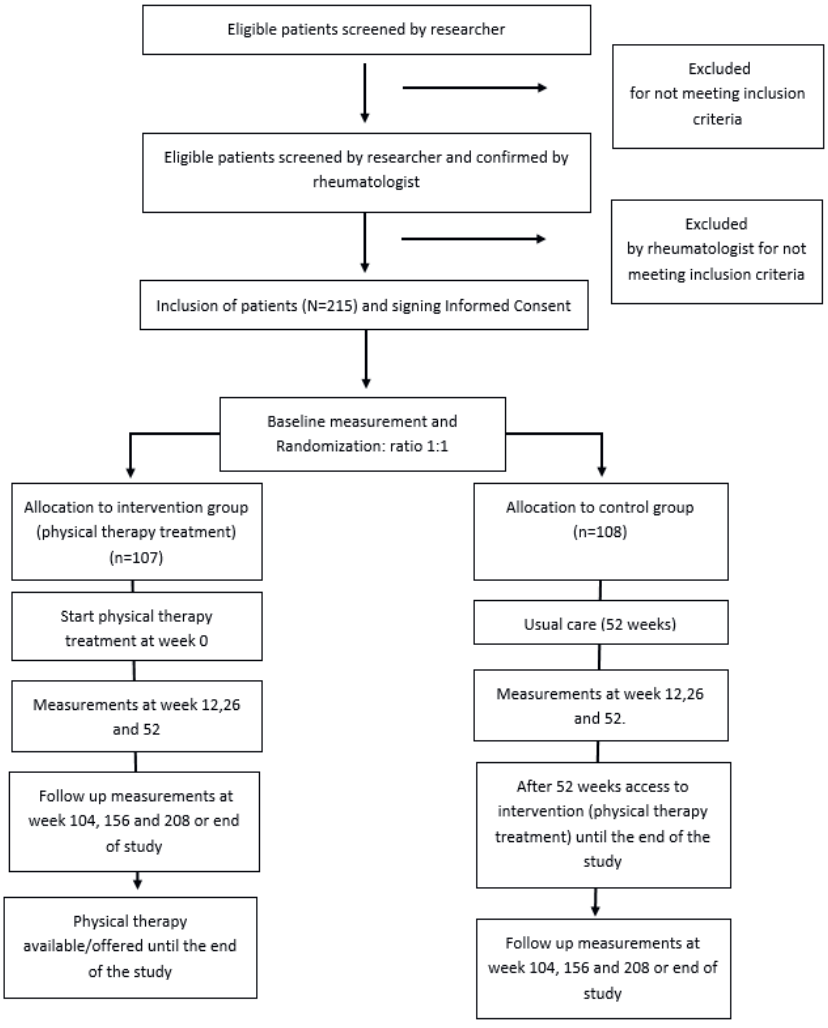
Methods

Study design

In two parallel nationwide RCTs, including either axSpA or RA patients with severe functional limitations in activities and participation, longstanding (≥52 weeks), active exercise therapy will be compared with usual care to evaluate its effectiveness and cost-effectiveness (L-EXSPA/L-EXTRA; Longstanding-EXercise therapy in patients with axSpA/ Longstanding-EXercise Therapy in patients with RA). Both RCTs are registered at the Netherlands National Trial Register: L-EXSPA (NL8235) and L-EXTRA (NL8238). The reporting of these studies is done in line with the CONSORT extension non-pharmacological studies [22].

The total duration of the studies is 208 weeks, with the duration of the inclusion period being 104 weeks. Assessments take place at baseline, 12, 26 and 52 weeks (primary endpoint). After the primary endpoint, patients in the usual care group are offered longstanding, active exercise therapy as well. In both groups, follow-up assessments take place at 104, 156 and 208 weeks or end of study. Participants are followed for a minimal period of 52 weeks and a maximum of 208 weeks. For participants entering the study in a later stage of the inclusion period, the follow-up will end before the maximum follow-up duration of 208 weeks. An overview of the studies is provided in the flowchart (Figure 1).

Figure 1 Study flowchart of two parallel studies for long-term exercise therapy in Axial SpondyloArthritis (axSpA) and Rheumatoid Arthritis (RA) patients.



Participants

The study populations consist of axSpA and RA patients with severe limitations in functioning (activities and participation). The definition of these populations was established in 2014 by an expert group of patient representatives, rheumatologists, health professionals and researchers, in collaboration with National Health Care Institute of the Netherlands. Our inclusion criteria are based on this definition.

Inclusion criteria:

1. Consenting adult patients diagnosed with axSpA or RA by a rheumatologist.
2. One or more severe functional disabilities despite adequate medical treatment of the rheumatic condition resulting in limitations in daily activities involving self-care (e.g., dressing, washing), transfers (e.g., getting in and out of bed, rising from a chair or using the toilet), and/or mobility indoors or outdoors.
3. Functional disability directly or indirectly related to the rheumatic condition, and caused by for example persisting or progressive high disease activity despite optimal medical treatment and/or severe joint damage and/or deformities and/or severe comorbidity (e.g., pulmonary or cardiovascular disease, depression, morbid obesity).
4. Functional disability can or could not be stopped or improved by a short, intermittent exercise therapy intervention.

Exclusion criteria:

1. Patients who received individual treatment of a physical therapist or a multidisciplinary team in the setting of a rehabilitation center or rheumatology clinic or center the last three months.
2. Patients in need of admission to a hospital, rehabilitation center or rheumatology clinic or other forms of intensive, multidisciplinary care.
3. Patients who are unable to give informed consent.

Study procedures

During the inclusion period (104 weeks), potential participants are informed by means of various media: websites, digital newsletters, flyers and (digital) posters. The Dutch Arthritis Society and the Dutch rheumatologists are involved in the recruitment of potential participants. Potential participants can register for the study via a registration link or the treating rheumatologists can register participants by contacting the researchers (MT, MvW; https://forms.lumc.nl/lumc2/aanmeldingsformulier-patient). As part of the procedure to screen the eligibility, the researcher first conducts a telephone interview with every patient that has registered. During that interview, a standardized list of relevant activities of daily living and the nature and extent of difficulties the patient experiences and their impact is discussed. The patient is then reviewed in a weekly conference with 4 members of the team

present. In case of doubt, additional questions are posed during another telephone interview. If it is concluded that the patient fulfills this and the other eligibility criteria, the rheumatologist is contacted to confirm the diagnosis and agree with the inclusion of the patient. After consent of the participant the treating rheumatologist is contacted to confirm the participants diagnosis. Participants meeting all inclusion criteria and with a written informed consent are included in the study.

Randomization and blinding

Randomization is executed by a research co-worker (WP, SvW), who is not involved in the assessments or data analysis. The randomization takes place in blocks of varying sizes (4-6-8 participants, size randomized) in a ratio of 1:1 and is stratified by gender and health care insurance status (Castor EDC. [2019]. Castor Electronic Data Capture). Randomization is stratified by gender and insurance status (0-11 vs. 12 or more sessions covered by additional health insurance), to make sure there will be no imbalance between the groups. For gender, the course of the disease and the effect of the treatment could be different between males and females [23, 24]. For insurance status, it is relevant that since 2012 exercise therapy is no longer covered in the basic health insurance for axSpA and RA patients in The Netherlands. The majority of patients has however an additional insurance to be able to cover the costs of physical therapy, with coverage varying with respect to the number of sessions that is reimbursed. An over-representation or under-representation of patients with (an extensive) coverage of exercise therapy in their additional health insurance in the control group could lead to relatively high or low usage of exercise therapy in that group and thus either decrease or increase the contrast with the intervention group. Given the nature of the intervention, participants and healthcare professionals involved in the treatment cannot be blinded to the treatment allocation and are instructed not to reveal information to the researchers regarding treatment allocation. The researchers are blinded to the allocation status, which is only revealed to them after the final statistical analysis. Participants are informed about their assigned condition after the baseline assessment by a research co-worker who is not involved in the assessments or analysis.

Intervention

Recruitment and training of therapists

The intervention is delivered by trained physical therapists (PTs) working in the surroundings of the participant's home and are recruited by a research co-worker (WP, SvW) who is not involved in the assessments. Recruitment mainly takes place through an existing national network of PTs with specific expertise regarding the treatment of patients with rheumatic and musculoskeletal diseases (RMDs; https://reumanetnl.nl/). To apply the treatment protocol, PTs are encouraged to comply with national recommendations for the physical therapy management of RA and axSpA [25, 26] and receive an 8-h training (combination of e-learning [4-h]), a scheduled, live online or face-to-face training (individual or small groups; 4-h and self-study). The training is provided by expert PTs in the project group (WP, SvW). The training contains specific information about the study protocol, the treatment procedures and how to tailor the treatment to the participant. Every PT has access to an e-learning app and receives a manual with similar information. Treating PTs may contact PTs with extensive expertise in this subpopulation with questions about the treatment protocol, tailoring the intervention, managing co-morbidities or other participant health problems. These experts PTs work in collaborating centers and have ample experience in treating patients with RMDs and severe limitations. In addition, interactive education sessions are held regularly to evaluate the intervention and to improve the treatment fidelity.

Content of the intervention

The intervention consists of longstanding (≥52 weeks), active exercise therapy aimed at improving individual limitations in daily activities and participation. Within 52 weeks, 64 treatments are planned, with two supervised treatments per week in the first 12 weeks. From week nine on participants are instructed and motivated to perform home-based exercises and increase physical activities in addition to the supervised treatments. An overview of the intervention is provided in Tables 1a and 1b. The intervention is reported in accordance with the Consensus on Exercise Reporting Template (CERT) [27]. The treatment is adapted to the individual participant, using a framework (based on 3iS strategy and Coach2Move program [28, 29]) to standardize the methods of initial assessment, setting treatment goals, clinical reasoning in monitoring participants' health status and treatment adjustment.

Table 1a Structure of the exercise therapy intervention.

Week	Session 1	Session 2
1	Anamnesis & physical examination	
2	Physical examination (if not finished yet) and goal setting	
3 – 8	Treatment	Treatment
9 – 12	Treatment and structural education/guidance in self-management of physical activity	Treatment and structural education/guidance in self-management of physical activity
13-52[a,b]	Treatment, exercise planning and education and self-management of physical activity	Optional, 14 additional treatments sessions can be scheduled in agreement with the participant

[a] Treatment can continue until 208 weeks or the end of the study.
[b] Evaluation and if necessary, adaptation of treatment plan and goals.

Table 1b Content of the exercise therapy intervention.

Individual active exercise training adapted to individual treatment goals. Exercise functions and activities, including:
Type: - *Aerobic training* Walking, biking, cross trainer, rowing and other (rhythmic) movements in which large muscle groups are used. - *Strength training* With use of own weight, attributes or devices. - *Functional training* Exercises that train motor skills such as balance or coordination, and activities of daily living; e.g. transfers, self- care, wash and dress oneself, housekeeping, and gait.
Timing: First 12 weeks, two times a week. After 12 weeks, one time per week with an option of 14 extra treatment sessions in the first year.
Dose of exercise: Duration of a training session is 30 min and intensity are based on the ACSM[a] guidelines. The training can be structured with increasing frequency, timing and intensity until the goal is achieved in steps of 5%-10% increase each week.
Guidance by physical therapist: Instructing, demonstrating and giving feedback.
Training location: The training will take place at a training center close to the participants home. Or at the home of the participant, depending on the physical limitations and ability to travel of the participant.
Individual counseling physical activity, informing, advising and educating:
Personal factors: Lifestyle/healthy behavior focusing on physical activity and optimal exercise level.
External factors: Exercises at home (execution, time and place).
Assistive product: Device that monitors the physical activity for motivation and behavioral change. Homework exercise program.

[a] American College of Sports Medicine (ACSM).

Every treatment session must consist of either a combination of functional training and aerobic training or functional training and strength training. These training sessions must meet the dosage (frequency, intensity and duration) and progression based on the American College of Sport Medicine guidelines for exercise prescription [30]. From week nine onwards, participants receive an activity tracker to monitor daily physical activity. Approximately every 12 weeks the treatment goals and the treatment plan are evaluated and adjusted accordingly. After a minimum of 52 weeks of therapy, the participant can continue the intervention until the end of the study. For each treatment session, PTs register process parameters, including the content of the applied treatment, training intensity, participant adherence, and side effects. These process parameters are used to tailor the treatment to participants' individual capabilities and are registered in OnlinePROMs® (2020, Interactive Studios BV).

Control (care as usual)

In the control group, the participants receive the usual care, to be determined by their treating physician(s) and participants themselves. After 52 weeks, the control group also has access to the intervention until the end of the study.

Outcome measures

The primary outcome is the difference between the intervention and control groups in changes in participants' reported limitations in functioning assessed by the Patient Specific Complaints Numeric Rating Scale (PSC NRS) [31, 32] at 52 weeks. The secondary outcomes of the two studies are divided into four categories: Daily Functioning (Function); Quality of life; Health care usage and costs (from the societal perspective) and Perceived effect and satisfaction with treatment. A detailed description of all outcome measures and their timepoints are shown in Tables 2a and 2b.

Table 2a Outcome measures at the different timepoints.

	Trial period				**Follow-up**		
Measures	T0 0 weeks	T1 12 weeks	T2 26 weeks	T3 52 weeks	T4 104 weeks	T5[c] 156 weeks	T6[c] 208 weeks
General Characteristics	X						
Primary outcome	X			X	X	X	X
Secondary outcomes							
a) Function	X		X	X	X	X[a]	X[a]
b) Quality of Life	X		X	X	X	X	X
c) Health care usage and costs	X	X	X	X	X	X	X
d) Perceived effect and satisfaction with treatment				X[b]	X[b]	X[b]	X[b]

[a] The 6MWT will not be measured at T5 and T6.
[b] In control group only if physical therapy has been used.
[c] Or end of study for participants included after 12 months after start of the study.

Table 2b Outcome measures and their description.

Measures	Description
General Characteristics	
Sociodemographic and disease characteristics; Comorbidity;	Age, gender, weight and height to calculate the Body Mass Index, status of living, level of education, insurance status, smoking, affected joints, joint surgery history, drugs and alcohol consumption and physical activity.
Primary outcome	
PSC NRS (Patient Specific Complaints Numeric Rating Scale)	The PSC NRS is an individualized outcome measure designed to detect changes in a client's perception of functioning and/or participation over time [31, 32]. It consists of three scales (NRS) indicating the level of difficulty patients encounter while executing activities that are most relevant for them ranging from 0 = easy, to 10 = impossible to do.
Secondary outcomes	
Function	
PROMIS-10 (Patient Reported Outcome Measurement Information System-10)	PROMIS is a standardized metric for measuring health across chronic diseases, developed using the item response theory [38-41]. The PROMIS Short Form v2.0 – Physical Function 10a will be used in this study to measure the patient reported physical function. It is a short questionnaire consisting of 10 questions. All questions have five answer options ranging from 1 = easy to 5 = impossible to do. From the raw score a T-score is derived, with the Dutch/Flemish population mean and a standard deviation. A high score indicates a poor patient reported physical function.
BASFI (Bath Ankylosing Spondylitis Functional Index)[b]	BASFI is a validated instrument to assess the degree of functional limitation in patients with axial spondyloarthritis [42, 43]. It comprises 10 questions on how well activities went in the past week. The questions are answered by a NRS, ranging from 0 = easy to 10 = impossible to do. The BASFI score is calculated by taking the mean of the score of the 10 individual questions. Scores can range from 0 to 10, with a high score referring to severe limitations.
HAQ-DI (Health Assessment Questionnaire-Disability Index)[c]	The HAQ measures functional ability in RA patients and comprises 20 questions regarding eight domains of activities of daily living with the total score ranging from 0 (no functional limitations) to 3 (serious functional limitations) [44-47].
6-Minute Walk Test[a]	The 6-min walk test is a performance-based test, in which the patient is requested to walk at a comfortable speed for 6 min, with the distance measured in meters. Patients are allowed to use a walking aid [33, 34]. According to the practice guideline for this instrument, the test is not used in case a patient cannot walk at all or needs a lot of support from another person in order to be able to walk.

Table 2b (Continued) Outcome measures and their description.

Quality of Life	
RA-QoL (Rheumatoid Arthritis Quality of Life questionnaire)[c]	The RA-QoL is a 30-item patient-based quality of life instrument specific for patients with RA. It was developed by researchers in the United Kingdom and The Netherlands and proved to be unidimensional, reliable and have good construct validity [48-50]. The RAQol comprises 30 statements, each with a yes/no response format. The overall score ranges from 0 to 30, with a high score indicating a poor QoL.
SF-36 (Short Form-36)	The Short Form-36 for Quality of life is a generic quality of life instrument [48, 51, 52] The 36 items are divided over 8 dimensions, from which 2 summary scales can be computed: The Physical Component and Mental Component Summary Scales (PCS and MCS), both with a score ranging from 0 (worst health status) to 100 (best health status).
EuroQol (EQ-5D-5L)	The EuroQol [53, 54] is a standardized instrument including 5 dimensions of health (mobility, selfcare, daily activities, pain/complaints and anxiety/depression), resulting in a score anchored at 0-1, with a higher score indicating better health. It also includes a visual analogue scale with a score ranging from 0 (worst possible health) to 100 (perfect health).
Health care usage and costs	
Health care usage and patient costs in the past months	Including General Practitioner visits, outpatient visits, hospital days, rehabilitation center, nursing home, home care, medication use, informal care, patient costs and productivity. Similar questionnaires have been used in previous studies on physical therapy in inflammatory arthritis [35].
Work status (paid and unpaid labor)	This questionnaire is constructed by the research group, including a health economist, containing questions regarding the current work status, the number of hours of work or volunteer work and the effect of the disease on the work of the participants. The questionnaire is based on questionnaires that were previously used in the RAPIT trial [35].
Perceived effect and satisfaction with treatment	
Perceived effect anchor question	Contains the anchor question on the perceived effect: "Has the exercise therapy changed your daily functioning?"
Satisfaction with longstanding exercise therapy	Short questionnaire on patient satisfaction with treatment, based on the Consumer Quality Index for physical therapy (CQ-Index) will be administered [55]. The questionnaire consists of questions regarding the satisfaction with the physical therapist, the treatment plan. Questions are open and multiple choice. A high score indicates a high satisfaction with the exercise therapy.
Perceived side effects of longstanding exercise therapy	A short-constructed questionnaire on patient satisfaction with treatment. The patient describes the perceived effect on for instance pain, functioning, daily activities on a 7-point Likert scale. Scores can range from 1 to 7 ranging, 1 = very much deteriorated to 7 = very much improved. A high score indicates an improved perceived effect.
Content of longstanding exercise therapy	A short questionnaire constructed by the research group to ask the patient about the content of the therapy he or she received.

[a] Performance measure.
[b] Measured only in the study population of axial spondyloarthritis patients.
[c] Measured only in the study population of rheumatoid arthritis patients.

Data collection

At baseline, general characteristics (e.g., age, gender, education level, length and weight) and disease specific characteristics are collected (e.g., the relevant medical history of the participant and exercises behavior). The individual level of functioning is measured with the PSC [31, 32] and the 6MWT [33, 34] and will be assessed at baseline, 52 weeks (primary endpoint), and at 104, 156 and 208 weeks or end of study. The 6MWT will be assessed by the researchers at baseline, 26, 52 weeks and at 104 weeks. The data will be stored in the online database OnlinePROMS©.

(Serious) Adverse Events

We defined a serious adverse event (SAE) as an untoward occurrence that results in death or is life threatening (at the time of the event), requires hospitalization or prolongation of existing in participants' hospitalization, or results in significant or permanent disability or incapacity. The SAE should be directly related to the exercise therapy treatment. All other untoward symptoms or complaints related to the exercise therapy treatment are defined as non-serious adverse events (AEs). Examples of non-serious AEs may include: falls without injuries, muscle injuries or any new occurrence of an unwanted unfavorable AE that is not defined as a SAE.

Serious and non-serious AEs are recorded and followed until they have abated, or until a stable situation has been reached. The assessors will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. All participants and therapists are asked to immediately and proactively report any AE or SAE to the assessors/researchers.

Sample size calculation

The primary measure of effectiveness is the PSC NRS at 52 weeks [30, 31] The threshold for discrimination for changes in patient reported outcomes in chronic diseases is an effect size of 0.5. Using a population effect size of 0.5 (alpha = 0.05, power of 0.90, two-sided, two-sample equal-variance t-test) 86 patients are required per group. Taking into account a 20% drop-out rate, we aim to recruit 215 patients per study.

Statistical analysis

Primary analysis

Effect on functioning

All primary analyses will be done based on the intention-to-treat principle. Using linear mixed models, for the primary outcome measure, changes on the PSC NRS at 52 weeks will be calculated (change in PSC as dependent variable and treatment condition [intervention or control] as independent variable). Adjustments will take place for baseline values, and if necessary, for unbalanced covariates. The assumptions of constant variance and linear relationships will be assessed. Transformations will be used when appropriate. Similar analyses will be done for the secondary outcome measures.

Cost-effectiveness

The economic evaluation will be a cost-utility analysis (CUA) from a societal perspective, with a 1-year time horizon, consistent with the Dutch guidelines (https://english.zorginstituutnederland.nl/publications/reports/2016/06/16/guideline-for-economic-evaluations-in-healthcare) and following the methodology of a previous CUA on long-term, dynamic exercise in RA [35]. Costs will be estimated from a societal perspective, including healthcare costs, patient costs, and productivity costs. Other costs will be calculated from cost questionnaires, with prices of healthcare Dutch standard prices and charges, as described in the Dutch guidelines. In the CUA, the impact on disease burden will be measured using quality-adjusted life years (QALYs) estimated from the Dutch tariff for the EQ-5D-5L at 0, 12, 26, and 52 weeks [36]. In the cost-effectiveness analyses, mean costs and patient outcome will be statistically compared, with multiple imputation to account for missing data. Costs will be related to patient outcomes using net-benefit analysis. Sensitivity analysis will be performed on the perspective of the cost analysis (societal vs. health care only) and the utility measure (Dutch EQ-5D-5L vs. Visual Analogue Scale).

Secondary analysis

Secondary analyses include a per protocol analysis. Moreover, an analysis with only those participants in the control group who did not or only to a small extent (8 sessions or less) used physical therapy will be performed. In addition, a mixed model analysis will be done taking into account all time points up to and including 52 weeks in order to compare the primary and all secondary outcome measures over time. The research question of the trials, determination of primary outcomes and the ensuing power calculation are all based on analysis of the whole group and not on specific subgroups.

Follow-up analysis

A follow-up is executed in both the intervention group and usual care group at 104 weeks and at 156 and 208 weeks after randomization or at the end of the study. This follow-up is done in order to monitor the longer-term effectiveness in the intervention group.

Adverse Events

The absolute number and the relative frequency of the SAEs and the AEs will be reported for both allocation groups. Also, a description of every occurred (S)AE is provided to give a complete overview of the events that occurred during the study.

Data management

All the data of the participants will be anonymized with assignment of a study number to every participant. The collected data will be stored for 15 years on a local drive at Leiden University Medical Center and a backup of the data will be stored at Data Archiving and Networked Services-The Royal Netherlands Academy of Arts and Sciences (DANS-KNAW; https://dans.knaw.nl/nl).

Discussion

There is a subgroup of patients with axSpA and RA (5%) with severe limitations in activities and participation despite medical treatment of the rheumatic condition, resulting from joint damage or persistent high disease activity, complications of the disease, its treatment or comorbidity. Despite the observed need for exercise therapy, research on effectiveness of longstanding, active exercise therapy in this particular subgroup is absent. By conducting two parallel RCTs, we aim to evaluate the effectiveness and cost-effectiveness of longstanding exercise therapy compared to usual care in the subgroup of patients with axSpA or RA and severe limitations in functioning. These two studies are first to investigate the effectiveness and cost-effectiveness of longstanding exercise therapy in this subgroup and the outcomes of these studies could lead to new knowledge and further improvement of the treatment. We hypothesize that longstanding, active exercise therapy in the described subgroups of patients with severe limitations is effective and cost-effective compared to usual care.

Implications on physiotherapy practice

The results of this research will result in new knowledge about the effectiveness and cost-effectiveness of longstanding exercise therapy for these specific subgroups, which should be implemented in physiotherapy guidelines. Physical therapists may use this knowledge in daily practice to improve the treatment of this subgroup.

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Authors contribution

Substantial contributions to the conception (C. H. M. van den Ende, M.G. J. Gademan, S. F. E. van Weely (SvW) and T. P. M. Vliet Vlieland) or design of the work (A. M. van

Tubergen, A. A. den Broeder, C. H. M. van den Ende, D. van Schaardenburg, M. G. J. Gademan, S. F. E. van Weely and T. P. M. Vliet Vlieland, W. F. Peter (WP) and W. B. van den Hout); AND Drafting the article or revising it critically for important intellectual content (A. A. den Broeder, A. M. van Tubergen, C. H. M. van den Ende, D. van Schaardenburg, M. G. J. Gademan, M. M. H. Teuwen (MT), M. A. T. van Wissen (MvW), S. F. E. van Weely and T. P. M. Vliet Vlieland, W. F. Peter and W. B. van den Hout);AND Final approval of the version to be published (A. A. den Broeder, A. M. van Tubergen, C. H. M. van den Ende, D. van Schaardenburg, M. G. J. Gademan, M. M. H. Teuwen, M. A.T. van Wissen, S. F. E. van Weely and T. P. M. Vliet Vlieland, W. F. Peter and W. B. van den Hout); AND Agreement to be accountable for appropriate portions of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (A. A. den Broeder, A. M. van Tubergen, C. H. M. van den Ende, D. van Schaardenburg, M. G. J. Gademan, M. M. H. Teuwen, M. A. T. van Wissen, S. F. E. van Weely and T. P. M. Vliet Vlieland, W. F. Peter and W. B. van den Hout).

Conflict of interest

The authors declare no conflict of interest.

Ethics and dissemination

The studies have been approved by the Medical Ethical Committee of the Leiden-Den Haag-Delft (METC LDD; L-EXSPA: NL70093.058.19, L-EXTRA: NL69866.058.19) and the two studies will be conducted in agreement with the declaration of Helsinki [37] and in compliance with the General Data Protection Regulations and the Dutch Medical Research Involving Human Subjects Act. Participants will have considerable time to decide whether they are willing to engage in the study. Written informed consent will be obtained from all engaged participants in the study. This study was classified as a low risk study by the METC LDD so that no Data safety Monitoring Board was put in place. The safety of the participants will be monitored by the online submission system of the METC LDD to report SAEs. SAEs will be reported within 24 hours after notification. The METC LDD will decide whether the safety of the participant is threatened and based on their judgement, the study can be continued or not. We intend to submit the results of the two studies in separate publications in peer-reviewed journals. Furthermore, we aim to present these results at international congresses and to disseminate the results to guideline committees.

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3

Chapter 3

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], Maaike G.J. Gademan[1,7]

1. Department of Orthopaedics, Rehabilitation and Physical Therapy, Leiden University Medical Center, Leiden, The Netherlands;
2. Department of Rheumatology, Sint Maartenskliniek, Nijmegen, The Netherlands;
3. Center for Rehabilitation and Rheumatology, Reade, Amsterdam, The Netherlands;
4. Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands;
5. Department of Research, Sint Maartenskliniek, Nijmegen, The Netherlands;
6. Department of Rheumatology, Radboudumc, Nijmegen, The Netherlands;
7. Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.

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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?Trial ID=NL8235).

Keywords: Rheumatoid arthritis; Physical function; Personalised care; Randomised controlled trial; Exercise.

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 RA [3] 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 randomized 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 rheumatology [20] 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 longstanding, 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 checklist [29] 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 goals [33] 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.reumanetnl.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 timepoints 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=mean difference intervention group–mean difference usual care group/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.

Figure 1 Flowchart.

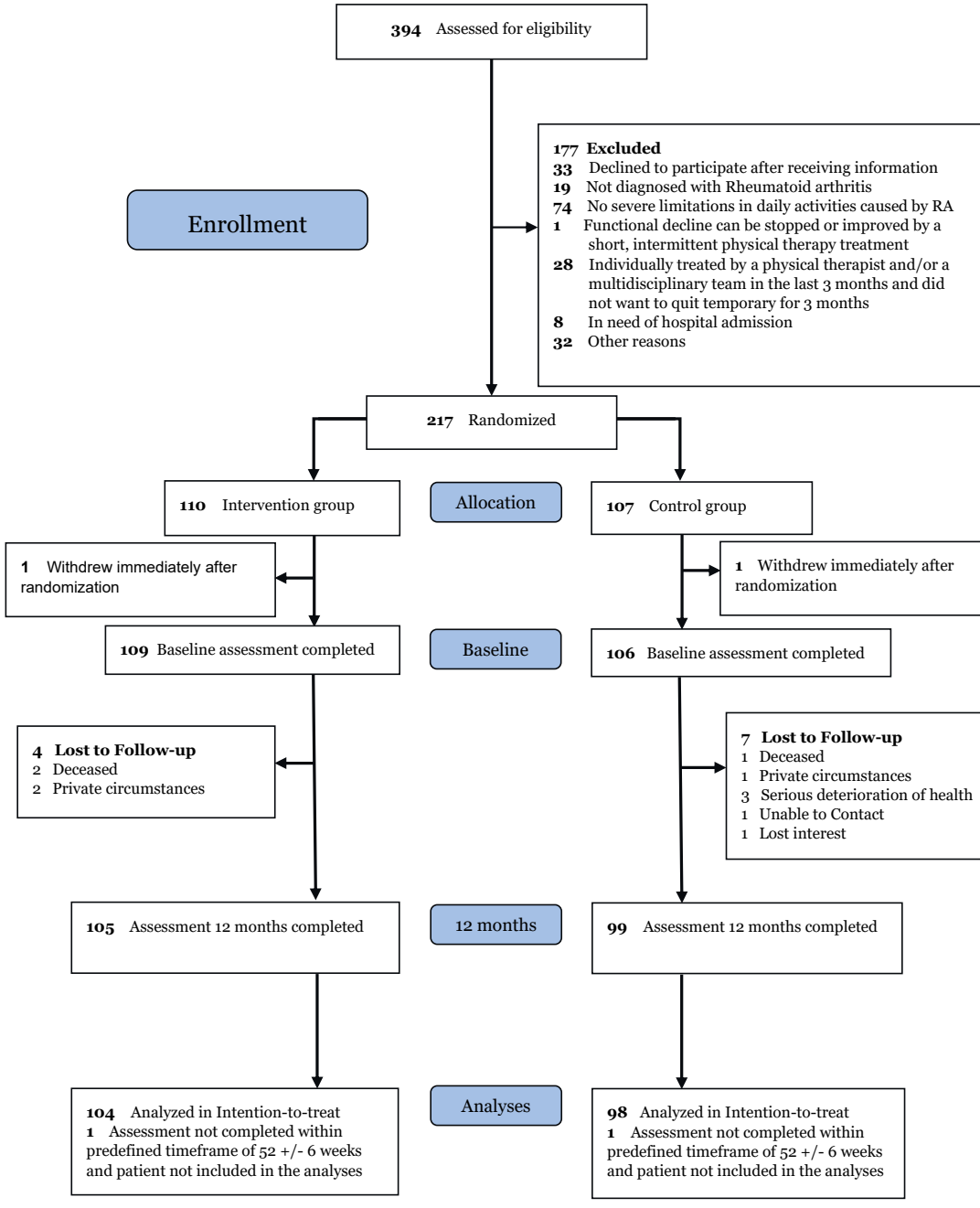

Table 1 Baseline demographics and disease characteristics of participants in a randomised controlled trial on longstanding, personalised exercise therapy.

	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/m2), 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[a], 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[b], 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[c], 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 intra-muscular/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)

BMI, Body Mass Index; ACPA, anti-citrullinated protein antibodies; DAS-28, Disease Activity Score; HAQ-DI, Health Assessment Questionnaire-Disability Index; DMARDs, Disease-Modifying Antirheumatic Drugs; Higher education, Bachelor or Master at University (of Applied Sciences); bDMARDS, biological Disease-Modifying Antirheumatic Drugs; tsDMARD, targeted synthetic Disease-Modifying Antirheumatic Drugs; csDMARD conventional synthetic Disease-Modifying Antirheumatic Drugs; NSAIDs, Non-Steroidal Anti Inflammatory Drugs.

[a] Difficult-to-treat RA definition based on Nagy et al. [4, 5].

[b] 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: DAS28-ESR=3.3928*Ln (DAS-28-CRP)+0.0254 [50]. The cut-off points of the DAS-28 score categories were based on Fleischmann et al. [28].

[c] Cut-off points of the HAQ-DI were based on Bruce et al. [42].

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.

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[c] in change scores between groups (95% CI)
N	104	104	104	98	98	98	202
Primary outcome							
PSC NRS 1[a] (0-10)	7.5 (1.3)	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[b] (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[b] (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[b] (meters)	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)

N, number of patients; SD, Standard Deviation; CI, Confidence Interval; PSC, Patient-Specific Complaints; NRS; numeric rating scale; 6MWT, Six Minute Walk Test.
[a] Primary outcome measure.
[b] Secondary outcome measures.
[c] Mean difference based on the unpaired Student's t-test.

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[b] between groups	
		N	mean (SD)	N	mean (SD)	β	95%CI
PROMIS	Baseline	107	33.6 (5.4)	104	34.2 (4.9)		
PF-10	26 weeks	92	35.7 (5.7)	90	33.9 (5.3)	2.42	[1.37, 3.46]
(13.5-61.9)	52 weeks	100	36.7 (6.2)	91	33.9 (6.0)	3.09	[1.80, 4.38]
HAQ-DI	Baseline	107	1.7 (0.5)	104	1.7 (0.5)		
(0-3)[a]	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]
RA-QoL	Baseline	107	16.7 (6.3)	104	15.5 (5.8)		
(0-30)[a]	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	Baseline	107	29.8 (7.6)	104	29.3 (8.2)		
PCS	26 weeks	91	31.9 (8.2)	90	29.1 (8.7)	2.28	[0.28, 4.28]
(0-100)	52 weeks	98	33.3 (8.9)	91	28.9 (9.6)	3.83	[1.49, 6.17]
SF-36	Baseline	107	46.2 (12.4)	104	47.4 (12.4)		
MCS	26 weeks	91	45.5 (12.4)	90	46.9 (11.6)	-0.31	[-2.90, 2.28]
(0-100)	52 weeks	98	47.8 (10.9)	91	46.5 (11.4)	2.54	[-0.47, 5.54]

N, number of patients; SD, Standard Deviation; CI; Confidence Interval; PROMIS PF-10, Patient Reported Outcome Measurement Information System Physical Function 10-Item Short Form; HAQ-DI, Health Assessment Questionnaire-Disability Index; RAQoL, Rheumatoid Arthritis Quality of Life; SF-36 PCS, 36-item Short Form Health Survey Physical Component Summary Score; SF-36 MCS, 36-item Short Form Health Survey Mental Component Summary Score.
[a] Lower score indicates better outcome. [b] Mean difference based on linear mixed model.

Harms

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

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 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.

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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.

Competing interests

None declared.

Ethics approval

This study involves human participants and was approved 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.

Supplementary files

- Supplementary Table 1: Patient involvement in a randomised controlled trial on the effectiveness of longstanding exercise therapy for patients with Rheumatoid Arthritis and severe functional disability.
- Supplementary Table 2: TIDieR (Template for Intervention Description and Replication) checklista describing a longstanding exercise therapy intervention for patients with rheumatoid arthritis (RA) and severe functional disability.
- Supplementary Table 3a: Outcome measures of effectiveness, their description and score ranges.
- Supplementary Table 3b: Schedule of assessments in a randomised controlled trial on longstanding exercise therapy compared with usual care in people with rheumatoid arthritis and severe functional limitations.

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Supplemental files

Supplementary Table 1 Patient involvement[a] in a randomised controlled trial on the effectiveness of longstanding exercise therapy for patients with Rheumatoid Arthritis and severe functional disability.

How was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences?
Patients were involved in the development of the research question in the sense that patient representatives from the national organisation Dutch Arthritis Society identified the need for a clinical study on the effectiveness of exercise therapy in patients with severe functional limitations. Two patient representatives took the initiative to apply for funding of such a study. In that process, they collaborated closely with representatives from the professional organisations of rheumatologists, health professionals in rheumatology, and physical and exercise therapists and with researchers. They have installed a steering group representing all of the abovementioned stakeholders (2016-2017).
How did you involve patients in the design of this study?
Two patient representatives from the national organisation were involved in all aspects of the study including the development of the research question, the study design, the intervention and outcome measures. For this purpose they organized and/or participated in regular meetings with the steering group, reviewed and contributed to all research documents and supported the complex administrative procedures. The national organisation has co-funded the development of the study (2017-2019).
Were patients involved in the recruitment to and conduct of the study?
The two representatives from the national organisation played an active role in the recruitment of patients by repeatedly disseminating information on the clinical trial via their website and social media channels. In addition, representatives from local or regional patient organizations actively supported the recruitment of patients. During the conduct of the study, the national patient representatives participated in / hosted the yearly steering group meetings. They contributed to the interpretation of the preliminary results of the study during the final steering group meeting. It was mutually agreed upon that they were not involved in the writing of the manuscript and so did not act as co-authors. The national organisation has co-funded the conduct of the study (2019-2023).
How will the results be disseminated to study participants?
The participating patients have been informed about the progress of the study throughout its execution, by means of electronic newsletters. The results will be disseminated to study participants by means of a personal electronic mailing. Moreover, the national organisation will play an active role in the dissemination of the results of the study to the larger group of patients with RA in The Netherlands. In addition, the representatives from the national organisation and individual patient representatives will be involved in a project aiming to develop a tailored implementation strategy for larger scale implementation (2023-2024).

[a] Staniszewska S, Brett J, Simera I, et al. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. BMJ. 2017 Aug 2;358:j3453.

Supplementary Table 2 TIDieR (Template for Intervention Description and Replication) checklist[a] describing a longstanding exercise therapy intervention for patients with rheumatoid arthritis (RA) and severe functional disability.

1. Brief name	Longstanding (52 weeks), personalised exercise therapy intervention for patients with RA and severe functional disability.
2. Why	Patients with RA and severe functional disability have been largely excluded from studies on the effectiveness of exercise therapy. It is likely that their needs are complex and may fluctuate over time, due to e.g. variations in disease activity, complications of the disease or its treatment and/or worsening of comorbid conditions. An intervention addressing the appropriate approach towards complex functional disability and is provided over a longer time period will suit the needs of those patients. The approach should follow both the framework of the International Classification of Functioning, Disability and Health (ICF)[b] and the Hypothesis Oriented Algorithm for Clinicians (HOAC)-II. [c d] The ICF provides health care professionals with a standardized framework to describe patients' functioning and external and personal factors that influence functioning on multiple domains in a common language. The HOAC-II model provides physical therapists with guidance in their clinical reasoning. The model is hypothesis oriented, which means that the physical therapist formulates hypotheses about the cause and consequence of the identified problems.
3. What (Materials)	*Intervention protocol: A* detailed intervention protocol was developed and a printed version was provided to every physical therapist taking part in a mandatory training on the delivery of the intervention. The content of the intervention protocol was based on a national physical therapy guideline on the management of RA[e] and treatment protocols for personalized exercise therapy in elderly patients with mobility problems[f g] and patients with knee osteoarthritis and multimorbidity.[h] The intervention protocol was developed by three physical therapists (WFP, SvW, MdR) who are experts in the treatment of people with rheumatic and musculoskeletal diseases and experienced in the design and clinical application of similar protocols for research purposes. The general design and the content of the intervention protocol were subsequently discussed in the steering group including patient representatives, rheumatologists, and primary care and expert physical therapists. In order to maintain the contrast in the study, the protocol was not available in an electronic format and participating physical therapists were instructed not to disseminate or show the protocol or its contents to others by any means. *Treatment registration forms:* Electronic forms to record the contents and evaluation of every treatment session, including the registration of possible (serious) adverse effects, were provided to participating physical therapists. *Wearable activity tracker:* Patients receiving the intervention were given a simple analog pedometer (Onmood, delivered by Bedrukken.nl) in order to monitor their physical activity level. Participating physical therapists were instructed to discuss the number of steps with patients receiving the intervention

Supplementary Table 2 (continued) TIDieR (Template for Intervention Description and Replication) checklist[a] describing a longstanding exercise therapy intervention for patients with rheumatoid arthritis (RA) and severe functional disability.

4. What (Procedures)	*Intervention* **a. Comprehensive assessment** The initial, comprehensive biopsychosocial assessment (history taking and physical examination) was based on recommendations in a national physical therapy guideline[e] with specific attention points related to complex RA and multimorbidity. [f-h] **b.Setting of treatment goals** The goal setting process comprised the elicitation of limitations in specific daily activities, their prioritization and subsequent setting of goals for desired treatment outcomes. [i] Formulation of goals should be SMART (specific, measurable, acceptable, realistic, timeline) **c.Treatment plan and modalities** Related to the treatment goals, the treatment plan was to be developed and agreed upon in collaboration with the participant. The selected treatment modalities should comprise two elements: Active exercises and patient education and self-management support. ***Active Exercises*** *Type:* Aerobic exercises *(*e.g. walking, biking, cross trainer, rowing and other (rhythmic) movements using large muscle groups); Muscle strengthening exercises (using own weight or devices); Neuromotor (functional) exercises (motor skills such as balance or coordination, training of specific activities of daily living such as transfers, self- care, washing and dressing oneself) *Dosage:* Duration of a treatment session 30 minutes, with the desired intensity based on the ACSM and EULAR recommendations for specific types of exercises. [j k] The intensity was increased progressively (approximately 5%-10% increase per week until desired level). ***Education and Self-management support*** Education on effective strategies to reduce functional disability or its progressions could include e.g. pacing of activities and rest, coping with pain and fatigue during and after activities and/or use of assistive devices); Promotion of health enhancing physical activity and support with acquiring and maintaining an optimal level of physical activity according to public health recommendations for health enhancing physical activity. [k] For this purpose, patients were given a wearable activity tracker and treating physical therapists were instructed to develop a personal movement plan or schedule. **d. Regular monitoring / evaluation** To ensure progress, the treatment goals and their attainment, the records of the treatment sessions and the level of physical activity were systematically evaluated every three months by the treating physical therapist. If necessary, the treatment goals and/or treatment plan could be adjusted in collaboration with the patient, to better meet the individual needs of the patient at a specific point in time.

Supplementary Table 2 (continued) TIDieR (Template for Intervention Description and Replication) checklist[a] describing a longstanding exercise therapy intervention for patients with rheumatoid arthritis (RA) and severe functional disability.

5. Who provided	Primary care physical therapists delivering the intervention were recruited through a national network of physical therapists with specific expertise regarding rheumatic diseases (www.reumanetnl.nl, accessed October 22, 2023). In case there was no member in the patient's residence, a physical therapist working in the neighbourhood, preferably with expertise regarding the treatment of people with rheumatic and musculoskeletal diseases or other chronic conditions was approached. *Training:* The training was mandatory and provided via live videoconferencing or via an App. The duration was 2.5 hours. The training consisted of 10 modules, 7 of which concerned the treatment and 3 the procedures related to the study (records of sessions and reimbursement processes). Before the training, participating physical therapists received the written intervention protocol. Attention points of the training were the process of clinical reasoning in complex health situations, including the presence of significant comorbidities; setting meaningful treatment goals; tailoring the content or dosage of treatment in case of changes in health status or worsening of symptoms after exercise; enhancing self-efficacy and self-management; giving feedback on progress; and identifying and using personal and environmental factors. The training was accredited by the national professional organizations of physical therapists. *Consultations with expert physical therapist:* All participating physical therapists could ask questions to and seek advice from an expert physical therapist (WFP) via online video consultation (organized twice per month) or e-mail. Examples include questions on the intervention protocol, tailoring of interventions to specific co-morbidities, or addressing other participant health concerns.
6. How	Face-to-face consultations, with online or telephone consultations in situations where face-to-face consultations were not possible (e.g. in case of COVID-19 restrictions).
7. Where	Primary care physical therapy practice in the neighbourhood/place of residence of the patient or at the patient's home.
8. When, and how much	First 12 weeks: two times per week. After 12 weeks: approximately one time per week, with an option of 14 extra treatment sessions over 52 weeks.
9. Tailoring	Physical therapists were instructed to continuously tailor the intervention to the patient's functional limitations and overall health status, including comorbidities. For that purpose, they were instructed to start every treatment session with an evaluation of the previous session, including possible adverse effects, and an inventory of any situations that could impact the content or dosage of treatment. Moreover, every 3 months the attainment of treatment goals was discussed between the treating physical therapist and the patient, and the treatment (goals, types of exercises, dosage, frequency of sessions) was adapted accordingly.
10. Modifications	Online or telephone delivery of treatment sessions due to COVID-19 restrictions.

Supplementary Table 2 (continued) TIDieR (Template for Intervention Description and Replication) checklista describing a longstanding exercise therapy intervention for patients with rheumatoid arthritis (RA) and severe functional disability.

9. How well (planned)	Delivery of the intervention: physical therapists' overall adherence to the intervention protocol was assessed by means of their periodic submission of mandatory reports from every session, where they recorded, amongst other characteristics of the treatment, the occurrence of any possible side effects, such as muscle pain or exertion. The submitted reports were checked and, if the content was not matching the treatment protocol or the information was lacking or incomplete, the physical therapists were contacted by an expert physical therapist (WFP and SvW) and given additional instructions. Moreover, there were bi-weekly digital meetings with the same experts where participating physical therapists could discuss any problems with the delivery of the intervention or their participation in the study.
10. How well (actual)	102 PTs were trained to deliver the intervention to the 109 patients in the intervention group, of whom 104 (95%) started the intervention. For 99 of these 104 patients the treating physical therapist handed in the treatment reports, in the other 5 no reports at all were submitted, despite several reminders and telephone contacts. Patients in the intervention group were using on average 39 sessions over 52 weeks (SD 15.9). Due to a logistical error, two patients (2%) in the usual care group were given access to the intervention and their physical therapists followed the mandatory training. One of these patients had 6 and the other 32 sessions.

[a] 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.
[b] 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 October 21, 2023].
[c] Schenkman M, Deutsch JE, Gill-Body KM. An integrated framework for decision making in neurologic physical therapist practice. Phys Ther 2006;86(12):1681-702.
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Supplementary Table 3a Outcome measures of effectiveness, their description and score ranges.[a]

Measures	Description
General Characteristics	
Sociodemographic and disease characteristics	Age; sex; weight and height to calculate the Body Mass Index; status of living; level of education; work status; insurance status; duration of complaints; years since diagnosis; fulfilling Difficult-to-Treat RA criteria[b c]; rheumatoid factor positive; anti-citrullinated protein antibodies (ACPA) positive; Disease Activity Score (DAS-28)[d e]; current use of Disease-Modifying Antirheumatic Drugs (DMARDs; bDMARDS, biological Disease-Modifying Antirheumatic Drugs; tsDMARD, targeted synthetic Disease-Modifying Antirheumatic Drugs; csDMARD conventional synthetic Disease-Modifying Antirheumatic Drugs); current use of Non-Steroidal Anti Inflammatory Drugs (NSAIDs), current use of oral glucocorticosteroids, current/recent glucocorticosteroid injection; ever smoked; joint surgery history, number of comorbidities.
Primary outcome	
PSC NRS (Patient Specific Complaints Numeric Rating Scale); Activity ranked 1.	The PSC NRS[f g] is an individualized outcome measure designed to detect changes in a client's perception of functioning and/or participation over time. It consists of three scales (NRS) indicating the level of difficulty patients encounter while executing activities that are most relevant for them ranging from 0 = easy, to 10 = impossible to do. The primary outcome measure is the NRS of the PSC of the limited activity ranked 1 (PSC1).
Secondary outcomes	
Function	
PSC NRS (Patient Specific Complaints Numeric Rating Scale); Activities ranked 2 and 3.	The PSC NRS[f g] is an individualized outcome measure designed to detect changes in a client's perception of functioning and/or participation over time (Beurskens et al., 1999; Stevens et al., 2017). It consists of three scales (NRS) indicating the level of difficulty patients encounter while executing activities that are most relevant for them ranging from 0 = easy, to 10 = impossible to do. The NRS of the PSC limited activities ranked 2 and 3 (PSC2 and PSC3) are secondary outcome measures.
PROMIS-10 (Patient Reported Outcome Measurement Information System-10)	PROMIS is a standardized metric for measuring health across chronic diseases, developed using the item response theory The PROMIS Short Form v2.0 – Physical Function 10a[h i] will be used in this study to measure the patient reported physical function. It consist of 10 questions. All questions have five answer options ranging from 1 = easy to 5 = impossible to do. From the raw score a T-score is derived. A higher score indicates a poorer patient reported physical function. The score ranges from 13.5-61.9).
HAQ-DI (Health Assessment Questionnaire-Disability Index)	The HAQ-DI[j k] measures functional ability in RA patients and comprises 20 questions regarding eight domains of activities of daily living with the total score ranging from 0 (no functional limitations) to 3 (serious functional limitations). HAQ-DI[l] scores 0-≤1 are classified as mild), >1--≤2 moderate-severe, and >2-≤3 as severe-very severe disability.
6-Minute Walk Test	The 6-min walk test[m] is a performance-based test, in which the patient is requested to walk at a comfortable speed for 6 min, with the distance measured in meters. Patients are allowed to use a walking aid. According to the practice guideline for this instrument, the test is not used in case a patient cannot walk at all or needs a lot of support from another person in order to be able to walk.

Supplementary Table 3a (continued) Outcome measures of effectiveness, their description and score ranges.[a]

Quality of Life	
RA-QoL (Rheumatoid Arthritis Quality of Life questionnaire)[c]	The RA-QoL[n o] is a 30-item patient-based quality of life instrument specific for patients with RA. It was developed by researchers in the United Kingdom and The Netherlands and proved to be unidimensional, reliable and have good construct validity. The RAQol comprises 30 statements, each with a yes/no response format. The overall score ranges from 0 to 30, with a higher score indicating a poorer QoL.
SF-36 (Short Form-36) Mental Component Summary Scale (MCS) and Physical Component Summary Scale (PCS)	The Short Form-36 for Quality of life is a generic quality of life instrument. The 36 items are divided over 8 dimensions, from which 2 summary scales can be computed: The Physical Component and Mental Component Summary Scales (PCS and MCS)[p q], both with a score ranging from 0 (worst health status) to 100 (best health status).

[a] A detailed description of outcome measures is also included in:
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(1):e1933.
[b] 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(1):20-33.
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Supplementary Table 3b Schedule of assessments in a randomised controlled trial on longstanding exercise therapy compared with usual care in people with rheumatoid arthritis and severe functional limitations.[a]

	0 weeks	**26 weeks**	**52 weeks**
General characteristics			
Sociodemographic and disease characteristics	X		
Primary Outcome Measure			
Functioning			
PSC (Patient Specific Complaints) NRS[b c] (Numeric Rating Scale); Activity ranked 1.	X		X
Secondary Outcome Measures			
Functioning			
PSC (Patient Specific Complaints) NRS[b c] (Numeric Rating Scale); Activities ranked 2 and 3.	X		X
PROMIS-10[d e] (Patient Reported Outcome Measurement Information System-10)	X	X	X
HAQ-DI[f g] (Health Assessment Questionnaire-Disability Index)	X	X	X
6-Minute Walk Test[h]	X		X
Quality of Life			
RA-QoL[i j] (Rheumatoid Arthritis Quality of Life questionnaire)	X	X	X
SF-36[k l] (Short Form-36); Physical and Mental Component Summary Scales (PCS and MCS)	X	X	X

[a] A detailed description of outcome measures is also included in van Wissen et al. 2022: 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(1):e1933: In contrast with the assessment schedule in that paper, the measurement of the 6-Minute Walk Test at 26 weeks was omitted for logistic reasons.

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[c] Stevens A, Koke 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(1):618.

[d] 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(3):304-14.

[e] Terwee CB, Roorda LD, de Vet HC, et al. Dutch-Flemish translation of 17 item banks from the patient-reported outcomes measurement information system (PROMIS). Qual Life Res 2014;23(6):1733-41.

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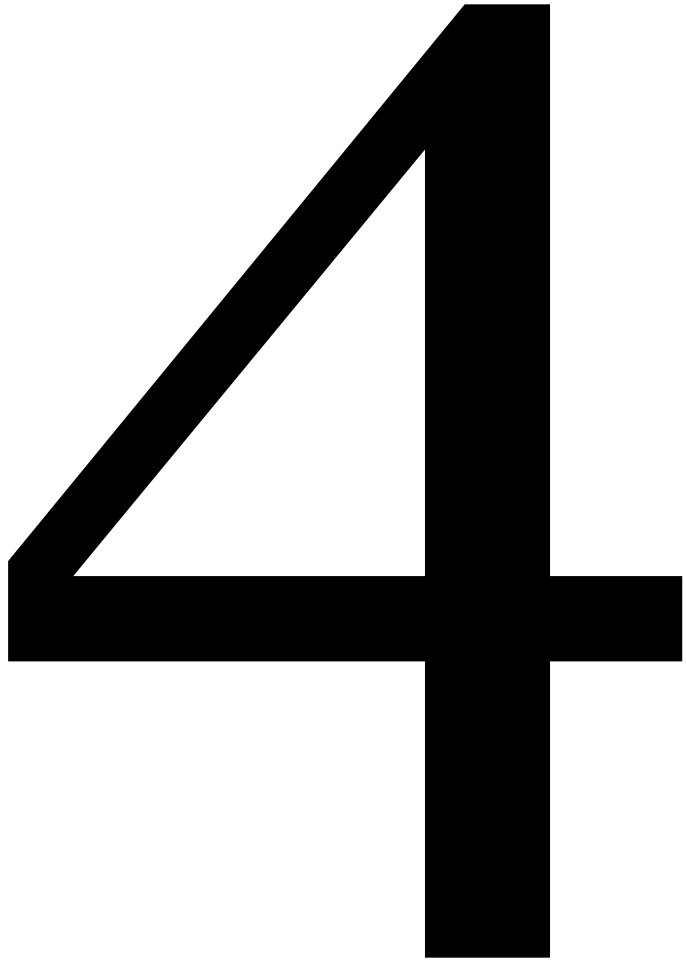
[j] de Jong Z, van der Heijde D, McKenna SP, et al. The reliability and construct validity of the RAQoL: a rheumatoid arthritis-specific quality of life instrument. Br J Rheumatol 1997;36(8):878-83.

[k] 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(11):1055-68.

[l] Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30(6):473-83.



Chapter 4

Cost-utility analysis of longstanding exercise therapy versus usual care in people with rheumatoid arthritis and severe functional limitations

Max M.H. Teuwen[1], Salima F.E. van Weely[1,2], Cornelia H.M. van den Ende[3,4], Maria A.T. van Wissen[1], Thea P.M. Vliet Vlieland[1], Wilfred F. Peter[1,5], Alfons A. den Broeder[6], Dirkjan van Schaardenburg[5], Maaike G.J. Gademan[1,7], Wilbert B. van den Hout[8]

1. Department of Orthopaedics, Rehabilitation and Physical Therapy, Leiden University Medical Center, Leiden, The Netherlands;
2. Institute of Allied Health Professions, HU University of Applied Sciences, Utrecht;
3. Department of Rheumatology, Radboud University Medical Center, Nijmegen, The Netherlands;
4. Department of Research, Sint Maartenskliniek, Nijmegen, The Netherlands;
5. Center for Rehabilitation and Rheumatology, Reade, Amsterdam, The Netherlands;
6. Department of Rheumatology, Sint Maartenskliniek, Nijmegen, The Netherlands;
7. Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands;
8. Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands.

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Abstract

Objectives: To evaluate the cost-effectiveness of longstanding personalized exercise therapy compared with usual care in people with rheumatoid arthritis (RA) and severe functional disability.

Methods: In this cost-utility analysis of a randomized controlled trial (n = 215), with 1 year follow-up, the study population comprised individuals with RA and reported severe difficulties in performing basic daily activities. Assessments were at baseline, 12, 26, and 52 weeks, with measurements of costs including medical and non-medical costs as recorded by patients and healthcare providers. Quality-adjusted life-years (QALYs) were estimated using the EuroQol 5 dimensions 5 levels (EQ-5D-5L) and EuroQol Visual Analogue Scale (EQ-VAS). Costs and QALY differences were analysed according to the intention-to-treat principle using cost-effectiveness acceptability curves.

Results: The 1 year societal costs were non-significantly in favour of the usual care group, with a small difference of €180 [95% confidence interval (CI) €−4493 to €4852]. The QALYs were non-significantly in favour of the intervention group, by 0.02 according to the EQ-5D-5L (95% CI −0.05 to 0.09) and by 0.04 according to the EQ-VAS (95% CI 0.00 to 0.08). For a willingness-to-pay threshold of €50 000 per QALY, the intervention was the cost-effective strategy with 60% certainty.

Conclusion: This economic evaluation showed no clear economic preference for either group, as the intervention costs were higher in the intervention group, but partly compensated by other cost savings and improved QALYs. Despite severe RA, patients had better clinical outcomes compared with usual care, suggesting no economic reasons to refrain from exercise therapy.

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

Keywords: Cost-Utility; Economic evaluation; Costs; QALY; Rheumatoid arthritis; Exercise therapy.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease with a substantial impact on the quality of life of individuals [1–3]. Current management treatment strategies include pharmacological and non-pharmacological treatments, with exercise therapy being one of the key elements [4-6]. Various studies have demonstrated positive effects of supervised exercise therapy on aerobic capacity, muscle strength, functional ability, overall quality of life and the cardiovascular risk of people with RA [7-13]. Based on this evidence, exercise therapy is advocated in various professional guidelines on the management of RA [4-6]. A recent randomized controlled trial (RCT) evaluated the effectiveness of long-term exercise therapy with usual care in RA patients with severe functional disability due to complex health problems [14, 15]. This study found that a personalized, active 52-week exercise program comprising education, exercises and promotion of physical activity was more effective than usual care, with a statistically significant effect on both measures of physical functioning and quality of life [14].

In addition to confirming the effectiveness of exercise therapy interventions, it is important to assess the cost-effectiveness. Integrating economic criteria helps to evaluate whether the additional health gains justify the extra healthcare resources needed. Studies have thus far provided limited information on the cost- effectiveness or cost–utility of exercise interventions in RA, as confirmed in a systematic review and meta- analysis [7]. Whereas several economic analyses of exercise therapy in RA were concerned with studies that did not compare a comprehensive exercise therapy intervention with usual care [16–19], one was conducted alongside a 104 week RCT comparing a high-intensity exercise programme with usual care in people with RA [20]. This study found higher medical costs and societal costs, without improvement of quality-adjusted life-years (QALYs), and was therefore deemed not cost-effective [20]. However, that study did not include patients with a specific indication for exercise therapy, it had a fixed delivery of two sessions per week, and the study took place over 20 years ago, hampering its generalizability to more recent clinical trials in RA patients with specific health problems.

A more relevant economic analysis in the context of the RCT in people with RA and complex functional problems [14] is an RCT on goal-oriented exercise therapy for frail older adults with mobility limitations [21, 22]. That study compared the (cost-)effectiveness of a patient-centred physical therapy strategy (Coach2Move) with standard treatment, showing

significant cost savings and improved QALYs [21]. Despite its promising results, this study was conducted in a population of frail elderly people with mobility problems, which may not be generalizable to people with RA and functional disability.

Given the lack of knowledge on the cost- effectiveness of exercise therapy in people with RA and severe functional limitations, the objective of the present study was to evaluate the cost-effectiveness of longstanding, personalized exercise therapy compared with usual care in people with RA and severe functional limitations.

Methods

Study design

We conducted an economic evaluation alongside a 52 week RCT (the L-EXTRA study) comparing personalized exercise therapy with usual care [14, 15]. The sample size of 215 patients was determined based on the primary outcome measure of the L-EXTRA study, i.e. the patient specific complaints. More information on the design of the study can be found in the published study protocol [15]. The cost–utility analysis, adhering to Dutch economic evaluation guidelines [23, 24], was coordinated by Leiden University Medical Center between October 2019 and June 2023. The study was approved by the Medical Ethical Review Board Leiden– Den Haag–Delft (METC-LDD, P19.052), registered in the Dutch Trial Register (ClinicalTrials.gov: NL8235), and all patients provided written informed consent.

Study population

The study population comprised people with RA and severe functional disability, defined as self-perceived difficulties in basic daily activities (for eligibility criteria, see Table 1). The definition of functional disability had been established by an expert group consisting of patients, rheumatologists, healthcare professionals, and researchers. In people with RA, functional disability has a well-established link with disease activity [25– 27], but it can also be due to other factors such as joint damage or comorbidities [25, 27]. In part, the population of people with RA and severe functional disability may overlap with those meeting the criteria of difficult-to-treat RA [5, 28, 29].

Table 1 Eligibility criteria for participation in the L-EXTRA (Longstanding EXercise Therapy in patients with Rheumatoid Arthritis and severe functional disability) study.

Inclusion criteria
1. Adults (aged ≥ 18 years) with a rheumatoid arthritis diagnosis confirmed by a rheumatologist.
2. Individuals who experienced severe limitations in basic daily activities, including self-care (e.g. dressing, washing), making transfers (e.g. getting into and out of bed, rising from a chair, using the toilet), and/or mobility indoors or outdoors.
3. Individuals whose limitations were directly or indirectly associated with their rheumatic condition, e.g. with persisting or progressive disease activity despite optimal pharmacological treatment, severe joint damage or deformities, and/or severe comorbidities (e.g. pulmonary or cardiovascular disease, depression, obesity).
4. Individuals whose functional limitations were unlikely to be improved by or resolved with a short exercise therapy intervention.
Exclusion criteria
1. Individuals who had been individually treated by a physical therapist currently or in the past 3 months, whether or not in the context of a multidisciplinary team intervention.
2. Individuals who needed imminent admission to a hospital or rehabilitation centre.
3. Individuals who were unable to provide informed consent.

Recruitment and selection procedures

During a 22-month recruitment period, study information was disseminated via various channels. To reach potential participants, information was shared through websites, digital newsletters, flyers, and posters. Rheumatologists and clinical nurse specialists received information via e-mails and presentations. In addition, information letters were mailed to potentially eligible RA patients at two centres (Sint Maartenskliniek, Nijmegen; and Reade, Amsterdam).

Patients with RA who were interested could register themselves or via their treating clinician. The screening for eligibility consisted of a telephone interview with one researcher and subsequent discussion with two other research team members. If they were unsure

about a patient's eligibility, the larger research team was consulted and/or the patient and/or the treating rheumatologist were contacted. For those patients fulfilling the eligibility criteria, the treating rheumatologist was asked to confirm the clinical diagnosis of RA.

Intervention and control conditions

The intervention consisted of personalized, supervised, longstanding (≥ 52 weeks) active exercise therapy. The intervention was delivered by trained primary care physical therapists working in the neighbourhood of the participants, either at the practice of the physical therapist or in the participant's home. The mandatory training for physical therapists was provided via an online education session or app. The intervention was provided according to a standardized treatment protocol, including initial assessment, setting of treatment goals, and provision of active treatment, with individual adjustments based on regular monitoring and evaluations. More details of the intervention protocol have been published previously [14, 15]. Participants randomized to the control group received usual care, to be determined by the treating clinician(s) and the patients. Usual care could include usual physical therapy, by referral or self-referral, but only if provided by a physical therapist who did not treat participants in the intervention group. After 52 weeks, participants in both the intervention and usual care groups had access to the intervention until the end of the study.

Assessments

Sociodemographic and disease characteristics

After enrolment, sociodemographic and health characteristics were collected from the patients using a questionnaire comprising questions on age (years); sex (male/female/ other); height (cm) and weight (kg), to calculate the body mass index (BMI); single person household (yes/ no); educational level [low/medium: primary or secondary (vocational) education; high: bachelor's or master's degree at a university (of applied sciences)]; if 66 years or younger, having a paid job (yes/no); additional health insurance coverage (yes/no); self- reported duration of complaints (years); Health Assessment Questionnaire Disability Index (HAQ-DI) score (0–3) [30]; smoking status, currently or ever smoked (yes/no); and presence of 19 different comorbidities (yes/no), based on a questionnaire developed by Statistics Netherlands [31]. In addition, the treating rheumatologist was asked to provide information on the fulfilment of the definition of difficult-to-treat RA (yes/no) [5, 29] and the years since diagnosis (years).

Utility measures and QALYs

Utility reflects the value of quality of life, on a scale anchored at 0 ('as bad as death') and 1 ('perfect health'). We measured utility in two ways, at baseline, and at 12, 26, and 52 weeks. Participants described their general health status using the EuroQol 5 dimension 5 levels (EQ-5D-5L) classification system [32]. From the EQ-5D-5L classification system, the Dutch utility index was calculated [33]. Also, patients rated their health status using the EuroQol Visual Analogue Scale (EQ-VAS), ranging from 0 to 100, where 0 indicates the worst imaginable health and 100 the best imaginable health [32, 33]. The obtained EQ-VAS values were transformed into a utility score using the power function $1 - (1 - (\text{EQ-VAS}/100))^{1.61}$ [34]. One-year QALYs are a commonly used measure to inform healthcare resource allocation decisions [35], and were calculated by the area under the curve of each of the utility measures over the follow-up period.

Costs

One-year societal costs were calculated at the 2023 price level. Participants filled out questionnaires at 12, 26, and 52 weeks on healthcare use, domestic help and informal care, and hours of paid working time, absenteeism, and presenteeism, and lost unpaid productivity [adapted from the institute for Medical Technology Assessment (iMTA) Medical Consumption Questionnaire and the iMTA Productivity Cost Questionnaire] [36, 37]. In the intervention group, physical therapists reported the number of sessions for each study participant. In addition, participants in the intervention group were asked about the number of sessions of physical therapy. When participants reported more physical therapy sessions than their physical therapist had registered, the difference was designated as the discrepancy between patient-reported and physical therapist-registered physical therapy. All physical therapy sessions reported by participants in the usual care group were counted as 'patient-reported physical therapy'. Where possible, healthcare was valued with Dutch standard prices [38, 39]; otherwise, market prices were used. Travel costs were calculated from the number of healthcare visits, combined with national averages on travel distance and means of transportation (24). Domestic help, informal care, and unpaid productivity were all valued at €17 per hour [24]. According to the friction method, paid productivity losses were valued at €42 per hour, with a maximum of 3 months productivity loss [24, 38, 39].

Statistical analysis

Data were analysed using IBM SPSS for Windows, version 25.0 (released 2017; IBM Corp., Armonk, NY, USA). All statistical comparisons were performed using standard unequal variance t-tests according to the intention-to-treat principle, meaning that data from participants were analysed according to the randomized treatment assignment. Multiple imputation with 100 imputed data sets was used to account for missing data and to preserve power and possibly reduce bias [40]. Cost-effectiveness acceptability curves were constructed to show the probability that the longstanding exercise therapy was cost-effective compared with usual care, depending on the societal willingness to pay (WTP) for an additional QALY. These curves were calculated as the one-sided p-value for the differences in Net Benefit = (WTP × QALY) – Costs, between the patients in the intervention and the usual care groups [41]. In the Netherlands, acceptable WTP levels range from €20 000 to €50 000 or €80 000 per QALY [42], with €50 000 per QALY considered most suitable for the current patient population. In the base-case economic evaluation, total societal costs were compared to QALYs based on the utility index calculated from the EQ-5D-5L. Incremental cost-effectiveness ratios were calculated as the difference in costs divided by the difference in QALYs but were not further formally analysed. Sensitivity analyses were performed by considering a different utility measure (EQ-VAS) and different cost measures (costs from a medical perspective and only intervention costs).

Results

In total, 215 participants were included in the study: 109 participants in the intervention group and 106 in the usual care group. The mean ± sd ages of participants were 59.4 ± 12.1 and 58.1 ± 13.6 years, the proportions of females were 89% and 92%, and the proportions of patients with one or more joint arthroplasties were 38% and 37% in the intervention and usual care groups, respectively. There were no relevant differences in baseline characteristics between the groups (Table 2). Over the course of the 1 year study, 11 participants discontinued their participation [14]. In terms of health resource utilization and productivity measurements, 7% of the data was missing, and for utility measurements, 5% of the data were missing.

Table 2 Baseline demographic and health characteristics of people with rheumatoid arthritis (RA) and severe functional limitations participating in a randomized controlled trial comparing the cost-utility of longstanding personalized exercise therapy with usual care.

	Intervention group (N=109)	Usual care group (N=106)
Female	97 (89.0)	97 (91.5)
Age in years	59.4 ± 12.1	58.1 ± 13.6
BMI (kg/m²)	27.2 ± 5.0	27.9 ± 6.9
Single-person household	30 (27.5)	37 (34.9)
Higher Education[a]	35 (32.1)	27 (25.5)
Work status		
≤66 years old	82 (75.2)	72 (67.9)
Paid job	*23 (28.0)*	*22 (30.6)*
No job, health problems	*32 (39.0)*	*29 (40.3)*
No job, other reasons	*27 (32.9)*	*21 (29.2)*
Health insurance with additional coverage	96 (88.1)	98 (92.5)
Self-reported duration of complaints (years)	21.6 ± 12.6	21.6 ± 14.0
Years since diagnosis (years)	18.0 ± 11.9 (N = 102)	19.7 ± 14.1 (N = 91)
Difficult-to-treat RA (EULAR criteria)[b]	44 (43.6) (N = 101)	46 (51.1) (N = 90)
HAQ-DI	1.7 ± 0.5	1.7 ± 0.5
Smoking status: ever smoked	60 (55.0)	68 (64.2)
Number of comorbidities	(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)

BMI, Body Mass Index; HAQ-DI, Health Assessment Questionnaire-Disability Index; RA, Rheumatoid arthritis.
Data are shown as n (%) or mean ± sd.
[a] Higher education: Bachelor or Master degree at University (of Applied Sciences).
[b] Difficult-to-treat RA definition based on Nagy et al. [29].

Table 3 Mean utility scores and QALYs, by time and group.

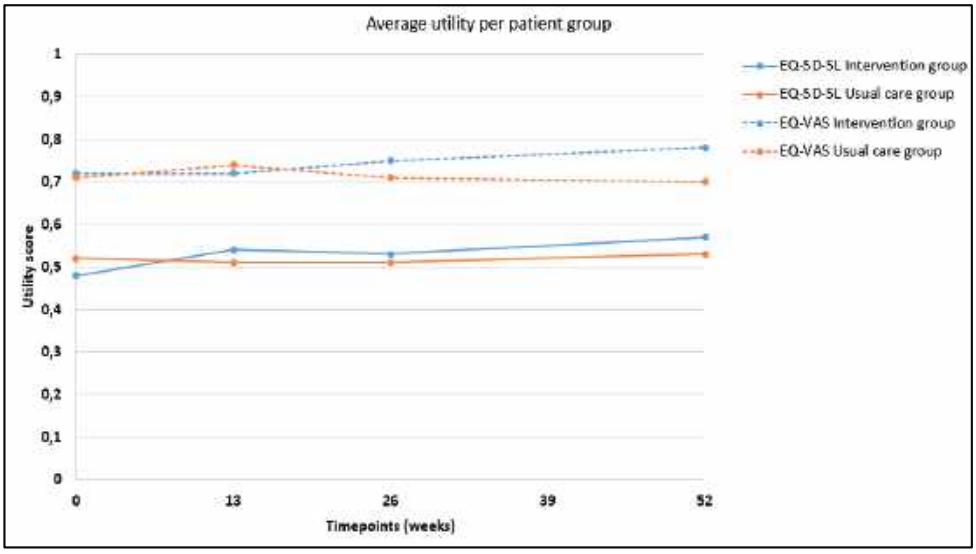
	Intervention group (n=109)	Usual care group (n=106)	MD[a]	95% CI	P[b]
EQ-5D-5L utility score					
Baseline	0.48 ± 0.28	0.52 ± 0.26	-0.04	-0.11 to 0.03	0.31
12 weeks	0.54 ± 0.28	0.51 ± 0.28	0.03	-0.04 to 0.11	0.42
26 weeks	0.53 ± 0.32	0.51 ± 0.27	0.02	-0.06 to 0.10	0.66
52 weeks	0.57 ± 0.29	0.53 ± 0.26	0.04	-0.03 to 0.12	0.28
QALY EQ-5D-5L	0.54 ± 0.25	0.52 ± 0.22	0.02	-0.05 to 0.09	0.54
EQ-VAS utility score					
Baseline	0.72 ± 0.19	0.71 ± 0.19	0.01	-0.04 to 0.06	0.66
12 weeks	0.72 ± 0.18	0.74 ± 0.19	-0.02	-0.07 to 0.03	0.43
26 weeks	0.75 ± 0.19	0.71 ± 0.19	0.05	-0.01 to 0.10	0.09
52 weeks	0.78 ± 0.16	0.70 ± 0.22	0.09	0.03 to 0.14	0.001
QALY EQ-VAS	0.75 ± 0.14	0.71 ± 0.16	0.04	0.00 to 0.08	0.08

MD, mean difference; EQ-5D-5L, EuroQol 5 dimensions 5 levels, EQ-VAS, EuroQol Visual Analog Scale with power transformation.
Data are shown as n (%) or mean ± sd.
[a] Mean Differences of the QALYs between intervention and usual care group.
[b] The P-values and 95%Cis are for the differences in QALYs between groups.

Utilities and clinical outcome

Table 3 reports the EQ-5D-5L and EQ-VAS at each time-point. The mean valuation of health for both utility measures after 1 year was more favourable in the intervention group than in the usual care group (Figure 1). However, with the exception of the difference in the EQ-VAS score at 52 weeks [0.09 point, 95% confidence interval (CI) 0.03 to 0.14, p = 0.001], none of the differences reached statistical significance.

Figure 1 Mean utility, by time and treatment group.



EQ-5D-5L, EuroQol 5 dimensions 5 levels; EQ-VAS, EuroQol Visual Analogue Scale.

Cost of exercise therapy

Table 4 shows the costs per patient in the intervention and usual care groups. The proportion of participants in the intervention group who had actually used the longstanding personalized exercise therapy intervention was 91%. The mean number of sessions based on the registrations of the physical therapists was 35 for the total group and 39 for the group who had used the intervention, with the large majority of treatments provided at the physical therapist's practice. The mean total costs of the intervention in the intervention group were €1423 ± 762 per patient. Compared to the registrations of the treating physical therapists, 46% of the participants in the intervention group reported more treatment sessions than the number registered by the physical therapist. This discrepancy could be due to underreporting by physical therapists, overreporting by patients, or the use of physical therapy outside the study intervention, although the last of these was discouraged. The mean costs of physical therapy that was reported by patients but not registered by physical therapists in the intervention group were €433 ± 722. In the usual care group, 66% of the participants reported the use of physical therapy other than the study intervention, with the mean costs per patient being €644 ± 852. Owing to a logistical error, two patients (2%) in the usual care group were also given access to the intervention within the 52 week period, resulting in mean costs of the intervention in the usual care group of €14 ± 127.

Table 4 Mean 1-year medical and non-medical costs per participant, by group.

	Intervention group (n=109)		Usual care group (n=106)		Difference in costs between groups		
	Volume	Costs (€)	Volume	Costs (€)	Difference (€)	95% CI	P
Physical therapy (visits)							
Intervention, at center[a]	87% 39	1361	2% 19	14	1346	1194 to 1499	<0.001
Intervention, at home[a]	2% 41	32	0% -	0	32	-14 to 78	0.17
Intervention, combination	2% 41	30	0% -	0	30	-12 to 72	0.16
Total intervention physiotherapy[a] (mean ± sd)	91% 39	1423 ± 762	2% 19	14 ± 127	1409	1264 to 1554	<0.001
Patient-reported physiotherapy[a]			66% 24	644	-211	-431 to 9	0.06
Discrepancy in patient-reported and physical therapist-registered physiotherapy[a]	46% 23	433					
Total physical therapy (mean ± sd)	98% 47	1856 ± 815	68% 24	659 ± 851	1198	967 to 1428	<0.001
General practitioner	5.5	194	6.4	222	-28	-79 to 24	0.29
Specialists							
Rheumatologist (visits)	4.3	477	4.2	467	10	-73 to 93	0.81
Orthopedic surgeon (visits)	0.9	104	1.0	114	-10	-57 to 38	0.69
Internist (visits)	0.7	77	0.4	39	37	0 to 75	0.05
Cardiologist (visits)	0.6	65	0.4	49	16	-20 to 51	0.39
Other (visits)[b]	3.0	336	2.1	235	101	-47 to 249	0.18
Other healthcare providers							
Rheumatology nurse (visits)	1.9	40	1.3	27	13	-6 to 32	0.18
Podiatrist (visits)	0.8	31	0.6	25	6	-11 to 23	0.50
Occupational therapist (visits)	0.9	34	1.0	40	-5	-47 to 34	0.78
Dietitian (visits)	1.0	36	0.6	22	14	-12 to 41	0.29
Social worker (visits)	0.3	27	0.4	32	-5	-41 to 32	0.80
Other (visits)[c]	1.3	93	1.4	57	36	-8 to 81	0.41
Day treatment hospitalizations							
Hospital (visits)	1.5	448	1.1	343	106	-140 to 351	0.40
Rehabilitation center (visits)	0.1	84	1.3	817	-733	-1926 to 461	0.23
Psychotherapeutic institution (visits)	1.5	350	2.1	490	-140	-636 to 357	0.58
Inpatient hospitalization							
Hospital (days)	2.3	1341	2.0	1168	173	-1107 to 1453	0.79
Rehabilitation center (days)	1.4	788	2.2	1255	-467	-1728 to 794	0.47
Psychotherapeutic institution (days)	0	0.0	0	0.0	-	-	-
Home care (h/week)	0.7	1575	0.7	1612	-37	-854 to 779	0.93
Medication							
bDMARDs	79%	6187	79%	5348	839	-678 to 2356	0.26
tsDMARDs	40%	2252	51%	2693	-441	-2626 to 1744	0.69
csDMARDs	81%	220	65%	170	50	-21 to 121	0.17
NSAIDs	65%	162	59%	146	16	-60 to 92	0.68
Corticosteroids	72%	14	65%	11	4	-1 to 9	0.13
Total medication costs (mean ± sd)	100%	8834 ± 8367	98%	8367 ± 8001	467	-2329 to 3264	0.74
TOTAL medical costs (mean ± sd)		16791± 11361		16038 ± 12454	754	-3012 to 4519	0.70

Table 4 (continued) Mean 1-year medical and non-medical costs per participant, by group.

	Volume	Costs (€)	Volume	Costs (€)		95% CI	P
Non-medical costs							
Working hours (h/week)	5.5		5.1				
Absenteeism (h/week)	1.3		0.7				
Presenteeism (h/week)	1.4		1.9				
Productivity cost	-	2447	-	2026	421	-1014 to 1856	0.57
Lost unpaid labor (h/week)	2.8	2446	3.3	2949	-503	-1909 to 904	0.48
Household help (h/week)	0.4	394	0.7	590	-196	-528 to 137	0.25
Informal care (h/week)	4.7	4157	5.1	4521	-364	-1786 to 1058	0.62
Travel costs physiotherapy		101		37	65	52 to 78	<0.001
Travel costs other healthcare		104		101	2	-22 to 26	0.84
TOTAL non-medical costs (mean ± sd)		9650 ± 9568		10224 ± 8788	-574	-3098 to 1950	0.66
TOTAL societal costs (mean ± sd)		26441 ± 16021		26261 ± 15321	180	-4493 to 4852	0.94

bDMARDS, biological Disease-Modifying Antirheumatic Drugs; tsDMARD, targeted synthic Disease-Modifying Antirheumatic Drugs; csDMARD conventional synthetic Disease-Modifying Antirheumatic Drugs; NSAIDs, Non-Steriodal Anti-Inflammatory Drugs.

[a] The reported number of visits reported here is the average among patients with at least one visit.

[b] Other healthcare specialist: i.e. surgeon, gynecologist, pulmonologist, dermatologist, neurologist, ophthalmologist, or urologist.

[c] Other healthcare providers: i.e., psychologist, nurse other than rheumatology specialist nurse, medical pedicure, speech therapist, skin therapist, or practice assistant.

Other medical and non-medical costs

The difference between the intervention and usual care groups in total 1 year medical costs was estimated to be €754 (95% CI €−3012 to €4519), non-statistically significantly in favour of the usual care group (Table 4). This difference was almost exclusively driven by lower inpatient and day-patient rehabilitation costs in the intervention group than in the usual care group, although these were not significantly different. Regarding the costs of medication, the estimated costs in both groups were the highest for biological and targeted synthetic disease-modifying anti-rheumatic drugs (bDMARDs and tsDMARDs), with overall relatively similar proportions of patients using specific types of DMARDs. In general, there were no differences in the estimated costs of medication between the intervention and usual care groups.

With respect to the 1 year non-medical costs, the difference between the intervention and usual care groups was estimated to be €−574 (95% CI €−3098 to €1950), non-statistically significantly in favour of the intervention group. Most of the non-medical costs were attributable to informal care, where more informal care costs were seen in the usual care group than in the intervention group; however, the difference was not statistically significant. There were also more costs in the usual care group for home help and lost unpaid labour, but the differences did not reach statistical significance. The mean total

societal costs per participant were estimated at €26 441 for the intervention group and €26 261 for the usual care group, with a difference in total societal costs of €180 (95% CI €−4493 to €4852) in favour of the usual care group. However, this overall difference was not statistically significant.

Cost-utility analysis

In the base-case cost–utility analysis, the total societal costs were somewhat more favourable in the usual care group, whereas QALYs based on the EQ-5D-5L were somewhat more favourable in the intervention group, although both differences were not statistically significant. As a result, the probability that the intervention is cost-effective is below 50% if QALYs are valued low (left-hand part of the acceptability curve in Figure 2) and is above 50% if QALYs are valued high (right-hand part in Figure 2). But, regardless of the WTP, this probability of cost-effectiveness remains close to 50%, ranging from 47% to 65%. For a WTP threshold of €50 000 per QALY, the intervention is 60% likely to be the cost-effective strategy. The point estimate for the incremental cost-effectiveness ratio is favourable at €9000 per QALY; however, this is a very unstable estimate with an infinite confidence interval, owing to the non-significant difference in QALYs. In the sensitivity analyses with QALYs calculated from the EQ-VAS, results were more in favour of the intervention group compared to QALYs calculated from the EQ-5D- 5L, with the acceptability curves showing a higher probability for the intervention to be cost-effective, especially for the higher WTP values. Alternatively, the narrower cost perspectives with only healthcare costs or only intervention costs resulted in larger and more statistically significant cost differences in favour of usual care. As a result, the acceptability curves show a lower probability for the intervention to be cost-effective, especially for the lower WTP values. At €50 000 per QALY, the intervention is 46–72% likely to be cost-effective. These results indicate that there is no clear economic preference for either the intervention or usual care: regardless of society's WTP for an additional QALY, both were about equally likely to be cost-effective.

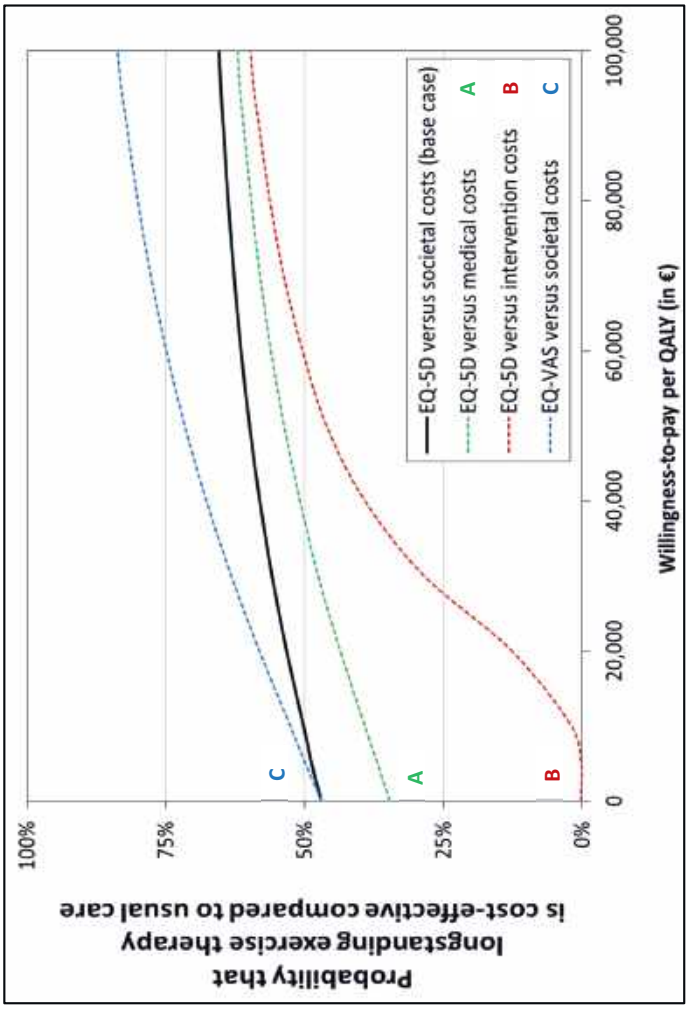


Figure 2 Cost-effectiveness acceptability curve showing the probability that longstanding personalized, supervised exercise therapy compared with the usual care programme is a cost-effective strategy over a range of values for the willingness to pay for an additional quality-adjusted life year (QALY).

EQ-5D-5L EuroQol 5 dimensions 5 levels; EQ-VAS EuroQol Visual Analogue Scale

Discussion

This economic analysis alongside a 52 week, assessor-blinded RCT, comparing the cost-effectiveness of longstanding personalized exercise therapy with usual care in people with RA and severe functional limitations, concluded with no clear economic preference for either the intervention or usual care. The total intervention costs were €1423, whereas the estimated total societal costs were €180 higher in the intervention than in the usual care group. This difference was small and not statistically significant, with a wide confidence interval owing to the high variability in costs (95% CI €−4493 to €4852). The intervention group had more favourable health valuations than the usual care group, although the differences were not statistically significant, except for the EQ-VAS at 52 weeks. The net-benefit analysis showed that there was no clear economic preference for either group. Regarding the existing literature, economic analyses of exercise therapy in RA have primarily focused on very specific exercise interventions: hand exercise [16], promotion of physical activity only [17], a comparison across two exercise interventions [18], or combinations of exercise with other treatment modalities [19]. Thus, a conclusion on the cost-effectiveness of comprehensive exercise therapy interventions, as advocated in professional guidelines on the management of RA [4–6], cannot be drawn. Only one other economic analysis on a somewhat similar intervention to that used in the present study, being a 104 week exercise therapy intervention comprising high-intensity aerobic and muscle-strengthening exercises, has been conducted in patients with RA. From that study, it was concluded that compared with usual care, the intervention provided insufficient improvement in the valuation of health to justify its extra costs [20]. An important difference from the present study is that the previous study included a different group of RA patients, not selected based on functional disability, with stable medication, and lacking weight-bearing joint prostheses or serious comorbidities [20]. Indeed, the utility scores of the patients included in the previous study were more favourable at baseline than those of the patients in the present study, potentially leading to smaller room for improvement. Moreover, the intervention in the previous study was different, as it concerned a group exercise therapy programme with a relatively fixed content and number of sessions for every patient, whereas the intervention in the current study was explicitly tailored to patients' individual needs. For these reasons, fair comparisons with the present study are difficult to make.

However, the economic analysis of an intervention that was used in the development of the exercise therapy intervention in the present study is of interest [21]. That study was conducted in another population, namely, elderly people with complex mobility problems, yet concerned an intervention tailored to individual patients' personal functional goals [21, 22]. Compared to usual care, the Coach2Move intervention yielded not only cost savings but also an effect on QALYs. Notably, in that study, all patients in the usual care group used physical therapy, whereas in our study the use of physical therapy was left to the discretion of the patient and/or clinicians. Thereby, the costs of physical therapy in the usual care group in our study were much lower than those in the Coach2Move study, making it more difficult to demonstrate the cost-effectiveness of the intervention.

The net costs in our study were slightly higher in the intervention group, primarily driven by the costs of the intervention. Although it could be hypothesized that this intervention may alleviate the necessity for expensive treatments, such as hospital or rehabilitation centre admissions, we were unable to establish any statistically significant difference in this aspect. In addition, while it is plausible that the intervention could improve work ability through enhanced functional capacity, we found no statistically significant difference in this aspect. Here, it must be noted that whereas 75% of the patients were of working age, only 30% of these had a paid job at enrolment. However, an ongoing study is evaluating a physical therapy intervention specifically aimed at working individuals with inflammatory arthritis, including RA [43].

Strengths of the current study include a low attrition rate and minimal missing values on utilities and cost- related assessments, enhancing the generalizability of the study results. In addition, the positive effects with respect to QALYs are in line with the proven benefits according to various self-reported and performance- based health outcomes in a separate analysis [14]. A limitation of our study is the 1 year time horizon; and the long-term effects in the context of continued use of exercise therapy need to be further investigated. Another limitation concerns the estimation of the costs of the intervention. There appeared to be a discrepancy between the number of sessions reported by patients and that registered by the physical therapists, possibly owing to overreporting by the patients (including the use of physical therapy other than the intervention), underreporting by physical therapists, or their combination. As we have no other means to verify the true number, the observed discrepancy cannot be resolved. In addition, the study focused on individuals with severe

functional limitations, with a mean disease duration of approximately 20 years, most of whom had low employment rates, potentially limiting the scope for improvement. However, results for individuals with milder functional limitations, who may require shorter and intermittent treatment, could be different. Another limitation relates to the generalizability of the results to healthcare settings other than the Netherlands, where access to physical therapy could be different, owing to variations in healthcare and insurance systems.

Conclusion

The results of this study showed no clear economic preference for either the intervention or usual care: the intervention costs were compensated by other cost savings and improved QALYs. However, underlining that the results apply to patients with longstanding, severe disease, despite which they experienced better clinical outcomes compared with usual care, the results of this study suggest that there are no clear economic reasons to refrain from longstanding exercise therapy in people with RA and severe functional limitations. Considering the severity and possible fluctuation of functional limitations over time, it is to be advised that patients should have permanent access to this intervention, with the actual usage tailored to their current needs.

Funding

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Author contributions

Substantial contributions to the conception and design of the work (SFE van Weely, CHM van den Ende, TPM Vliet Vlieland, MGJ Gademan, WB van den Hout); analysis and interpretation of the data (MMH Teuwen, SFE van Weely, CHM van den Ende, MAT van Wissen, TPM Vliet Vlieland, MGJ Gademan, WB van den Hout); drafting the article or revising it critically for important intellectual content (MMH Teuwen, SFE van Weely, CHM van den Ende, MAT van Wissen, TPM Vliet Vlieland, WF Peter, AA den Broeder, D van Schaardenburg, MGJ Gademan, WB van den Hout); final approval of the version to be published (MMH Teuwen, SFE van Weely, CHM van den Ende, MAT van Wissen, TPM Vliet Vlieland, WF Peter, AA den Broeder, D van Schaardenburg, MGJ Gademan, WB van den Hout); and agreement to be accountable for appropriate portions of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (MMH Teuwen, SFE van Weely, CHM van den Ende, MAT van Wissen, TPM Vliet Vlieland, WF Peter, AA den Broeder, D van Schaardenburg, MGJ Gademan, WB van den Hout).

Ethics

The L-EXTRA study was approved by the Medical Ethical Committee of the Leiden-Den Haag-Delft (METC LDD; L-EXTRA: NL69866.058.19) and the study is conducted in agreement with the declaration of Helsinki (2013) and in compliance with the General Data Protection Regulations and the Dutch Medical Research Involving Human Subjects Act. Written informed consent was obtained from all participants in the study.

Supplementary files

- Supplemental file 1: CHEERS 2022 Checklist

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Supplemental files

Supplemental file 1 CHEERS 2022 Checklist.

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Abstract
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Introduction
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Methods, 1st paragraph (Study design)
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Methods, 2nd paragraph (Study population)
Setting and location	6	Provide relevant contextual information that may influence findings.	Methods, 1st & 2nd paragraphs (Study design & Study population)
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Methods, 3rd paragraph (Intervention and control condition)
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Methods, 5th and 6th paragraphs (Utility measures and QALYs, Costs)
Time horizon	9	State the time horizon for the study and why appropriate.	Methods 6th paragraph (Costs)
Discount rate	10	Report the discount rate(s) and reason chosen.	N.A. (because of the short two-year time horizon)

Supplemental file 1 (continued) CHEERS 2022 Checklist.

Topic	No.	Item	Location where item is reported
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Methods, 4th, 5th, 6th paragraphs (Assessments, Utility measures and QALYs, Costs)
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Methods, 4th, 5th, 6th paragraphs (Assessments, Utility measures and QALYs, Costs)
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Methods, 4th, 5th, 6th paragraphs (Assessments, Utility measures and QALYs, Costs)
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Methods, 4th, 5th, 6th paragraphs (Assessments, Utility measures and QALYs, Costs)
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Methods, 6th paragraph (Costs)
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Methods, 7th paragraph (Statistical analysis)
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Methods, 7th paragraph (Statistical analysis)
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Methods, 7th paragraph (Statistical analysis)
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Methods, 7th paragraph (Statistical analysis)
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Methods, 7th paragraph (Statistical analysis) and Figure 2.

Supplemental file 1 (continued) CHEERS 2022 Checklist.

Topic	No.	Item	Location where item is reported
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Methods, 1st paragraph (Study design)
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	All paragraphs throughout the results and in Tables 1, 2 and Figures 1 and 2.
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	All paragraphs throughout the results and in Tables 1, 2 and Figures 1 and 2.
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	All paragraphs throughout the results and in Tables 1, 2 and Figures 1 and 2, except for the discount rate which is N.A.
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Methods, 1st paragraph (Study design) and Discussion, limitations section
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Discussion

Supplemental file 1 (continued) CHEERS 2022 Checklist.

Topic	No.	Item	Location where item is reported
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	End of manuscript
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	End of manuscript

From: Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force. Value Health 2022;25. doi:10.1016/j.jval.2021.10.008

II

Part II

Value of various outcome measures for effectiveness and safety of exercise therapy in people with inflammatory arthritis

5

Chapter 5

Functional limitations of people with rheumatoid arthritis or axial spondyloarthritis and severe functional disability: a cross-sectional descriptive study

Max M.H. Teuwen[1], S.F.E. van Weely[1], Thea P.M. Vliet Vlieland[1], Thom Douw[2], Dirkjan van Schaardenburg[3], Alfons A. den Broeder[4], Astrid M. van Tubergen[5,6], Maria A.T. van Wissen1, Cornelia H.M. van den Ende[7,8], Maaike G.J. Gademan[1,9]

1. Department of Orthopaedics, Rehabilitation and Physical Therapy, Leiden University Medical Center, Leiden, The Netherlands;
2. University of Applied Sciences Leiden, Leiden, The Netherlands;
3. Department of Rheumatology, Center for Rehabilitation and Rheumatology, Reade, Amsterdam, The Netherlands;
4. Department of Rheumatology, Sint Maartenskliniek, Nijmegen, The Netherlands;
5. Department of Rheumatology, Maastricht University Medical Center, Maastricht, The Netherlands;
6. Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands;
7. Department of Rheumatology, Radboud University Medical Center, Nijmegen, The Netherlands;
8. Department of Research, Sint Maartenskliniek, Nijmegen, The Netherlands;
9. Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.

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Abstract

Objectives: The objective of the study is to describe the nature of functional limitations in activities and participation in people with Rheumatoid Arthritis (RA) or axial SpondyloArthritis (axSpA) with severe functional disability.

Methods: Baseline data from people with RA (n = 206) or axSpA (n = 155) and severe functional disability participating in an exercise trial were used. Their three most limited activities were derived from the Patient Specific Complaint (PSC) instrument and linked to the International Classification of Functioning and Health (ICF). The frequencies of ICF categories were calculated and compared with Activities and Participation items of the ICF Core Sets for RA (32 second-level categories) and Ankylosing Spondylitis (AS) (24 second-level categories).

Results: In total 618 and 465 PSC activities were linked to 909 (72 unique in total; 25 unique second-level) and 759 (57 unique in total; 23 unique second-level) ICF categories in RA and axSpA. Taking into account all three prioritized activities, the five most frequent limited activities concerned the ICF chapter "Mobility", and included "Walking" (RA and axSpA 2 categories), "Changing basic body position" (RA and axSpA 1 category), "Stair climbing" (RA) and "Grasping" (RA),"Lifting" (axSpA) and "Maintaining a standing position" (axSpA). In RA, 21/32 (66%) and in axSpA 14/24 (58%) unique second-level categories identified in the prioritized activities are present in the Comprehensive Core Sets.

Conclusion: Most limitations of people with RA or axSpA and severe functional disability were seen in the ICF chapter "Mobility". Most of the identified ICF categories were covered by the corresponding items of the ICF RA and AS Core Sets.

Keywords: Rheumatoid arthritis; Axial spondyloarthritis; International classifcation of functioning, disability and health; Patient-reported outcome measures; Difficult-to-treat.

Introduction

Rheumatoid Arthritis (RA) and axial SpondyloArthritis (axSpA) are two prevalent forms of Inflammatory Arthritis (IA) and can both have a major impact on physical functioning, including limitations in daily activities and participation [1, 2]. The treatment consists of pharmacological and non-pharmacological interventions, with significant advancements in the pharmacological treatment options in recent decades [3, 4]. However, a subgroup of people with RA/axSpA has suboptimal treatment outcomes, which is reflected in the recent recognition of difficult-to-treat RA [5]. Some people with RA/axSpA still face severe functional disability despite optimal pharmacological treatment, stemming from joint damage accumulated over time, comorbidities or other health problems related to their rheumatic condition.

The optimal treatment of RA/axSpA requires shared decision-making between patients and clinicians, with goal-setting playing a crucial role [6, 7]. Literature on patient centered care emphasizes that treatment should address not only disease activity but also patients' functional limitations [6, 7]. A cross-sectional study, involving people with RA, found that 62% of the patient–clinician pairs achieved concordance on prioritization of the treatment goal "have fewer problems doing daily activities" [8]. This highlights the importance of considering patients' functional limitations when setting treatment goals. Despite the importance of addressing and prioritizing functional limitations as a treatment goal, there is limited literature on this topic. A systematic literature review, including 22 studies on treatment goal-setting for people with RA, identified functional limitations as a common theme within the physical experience of RA [9]. Goals on functional limitations included bending, engaging in physical activities and mobility [9]. However, none of the studies in that systematic review specifically included patients with severe functional disability. Such patients are likely to be represented in rehabilitation settings. In one study, a cross-cultural comparison between four countries of the contents of rehabilitation goals of people with RA admitted for rehabilitation was made [10]. In this, the rehabilitation goals were linked to the International Classification of Functioning, Disability and Health (ICF) [11] and ICF Core Set for RA [12], which includes the list of essential categories relevant to this specific health condition and health care context. It was found that most treatment goals were related to the ICF component "Activities and Participation" and fell within the chapters of "Mobility", "Self-care", and "Learning and applying knowledge" [10]. The contents of the rehabilitation goals were, to a considerable extend, covered by the Comprehensive ICF Core

Set for RA [10]. However, the generalizability of the results to the current populations of people with RA/axSpA and severe functional disability may be limited [10]. This study was conducted ten years ago, in which (pharmacological) treatments have evolved and are more treat-to-target, the methods used to achieve treatment goals differed between countries and data are only available from people with RA.Nowadays in the Netherlands, most people with RA/axSpA and severe functional disability requiring rehabilitative care are treated in primary care, with physical therapy being the most used intervention. Currently, there are instruments available for goal-setting in treatment, such as an instrument developed for people with RA and clinicians [8]. Additionally, several goal-setting instruments suitable for rehabilitation settings have been evaluated in people with RA as well. These include the Rehabilitation Activities Profile (RAP) [13], the Canadian Occupational Performance Measure (COPM) [14], and the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) [15].

Within the Dutch physical therapy community, the Patient Specific Complaint instrument (PSC) [16-20] is currently recommended. With the PSC, limitations in activities are identified and prioritized. The three highest ranked (and potentially modifiable) limitations in activities are scored on a 11-point numeric rating scale (anchors 0; no limitations—10; unable to perform) allowing evaluation over time [16-18].

Considering the limited knowledge regarding the nature of functional limitations of people with RA/axSpA and severe functional disability receiving physical therapy in primary care, this study aims to describe functional limitations in activities and participation of this subpopulation using the ICF as a reference. Insight into their prioritized functional limitations could facilitate the setting of treatment goals for daily activities.

Methods

Study design

This cross-sectional study concerns a descriptive analysis of the baseline data of two parallel randomized controlled trials (RCTs) investigating the effect of longstanding exercise therapy in primary care in people with RA or axSpA and severe functional disability (International Clinical Trials Registry Platform (ICTRP): Longstanding EXercise Therapy in patients with Rheumatoid Arthritis (L-EXTRA;NL8235) and Longstanding EXercise therapy in patient with axial SPondyolArthritis (L-EXSPA; NL8238)). All patients signed a

written informed consent form and both studies were conducted in agreement with the Declaration of Helsinki (2013) [21]. The ethical approval was granted by the Medical Ethical Committee Leiden-Den Haag-Delft (METC LDD; L-EXTRA: NL69866.058.19, L-EXSPA: NL70093.058.19). Details of both studies were published previously [22]. For this analysis, baseline data from the included patients available on 14 February 2022 were used. The study was reported according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting cross-sectional studies.

Participants

The inclusion and exclusion criteria of the RCTs have been published previously [22]. In brief, severe functional disability was defined as having self-perceived problems in performing basic activities of daily life (e.g. walking, dressing, washing oneself, using the toilet, preparing a meal, transfers). The problems should be related to their rheumatic condition, e.g. being due to persistent high disease activity, joint damage and/or deformities, complications of treatment, or co-morbidity. After patients had shown interest in the study, the presence of severe functional disability was to be confirmed during a structured telephone interview with one of the researchers (MT or MvW). In case of doubt, cases were presented and discussed in a larger team of researchers and clinicians to make the final decision on eligibility. If needed, additional information was requested from the patient or treating rheumatologist. After the screening, the treating rheumatologist was asked to confirm the diagnosis RA/axSpA of all eligible participants.

Assessments

Sociodemographic and disease characteristics

The baseline sociodemographic and disease characteristics were collected using a patient self-reported questionnaire containing questions on age (years), sex (male/female/other), body mass (kg), and length (meters) to calculate the body mass index (BMI), current medication use non-steroidal anti-inflammatory drugs (NSAIDs), any disease-modifying anti-rheumatic drug (DMARD) (categorized into conventional DMARD, biologic DMARD, targeted synthetic DMARD), or no anti-rheumatic medication or anti-inflammatory medication used), self-reported symptom duration (years), number of joint replacements, education level (low: primary school or pre-vocational secondary education; medium: senior general secondary education or pre-university education or secondary vocational education; high: Bachelor or Master at University (of Applied Sciences)) and, if 66 years or

younger, having a paid job (yes/no). Comorbidities were recorded based on a questionnaire developed by Statistics Netherlands, asking for the presence of 19 different comorbidities (yes/no) [23]. Moreover, we requested the treating rheumatologist to provide measures of disease activity in terms of the Disease Activity Score 28 (DAS-28) for RA and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for axSpA. These measures were collected as close as possible to the date of the participant's enrollment in the study. All baseline data were tested for normality using the Kolmogorov–Smirnov or similar test, where appropriate.

Physical functioning measures

Physical functioning was measured using three different questionnaires: the Patient-Reported Outcomes Measurement Information System—Physical Function item bank 10 (PROMIS PF-10) [24] was used in both populations, the Health Assessment Questionnaire—Disability Index (HAQ-DI) [25] in people with RA and the Bath Ankylosing Spondylitis Functional Index (BASFI) in people with axSpA [26].

The PROMIS PF-10 [24] comprises ten questions from the PROMIS physical function item bank, which all are scored on a five-point scale ranging from 1 to 5 with higher scores indicating better physical functioning. The total score was calculated by uploading the data into a scoring system program [27], after which the T scores are calculated. The PROMIS PF-10 can range from 13.5 to 61.9 [28], where a higher score indicates better physical functioning. A validated Dutch version was used and, calculations of T scores were standardized to the Dutch population [29].

The HAQ-DI [25] contains 20 items concerning the ability to perform daily activities, divided over eight domains. There are four possible responses and corresponding scores for each question (without any difficulty; score = 0, with some difficulty; score 1, with much difficulty score = 2, and unable to do score = 3). The highest score reported by the patient for any component question in each domain determines the score for that domain. A validated Dutch translation of the HAQ-DI was used [30]. The total HAQ-DI score was calculated by the sum of the scores of the eight domains divided by eight, after correcting for the use of aids or devices [25]. While there is no data evidence as to what constitutes mild, moderate, or severe disability, a score of ≤ 1.0 is regarded as indicating mild disability, and a score ≥ 2.0 is considered to indicate severe disability [31].

The BASFI is a validated instrument to assess the degree of functional limitation in patients with Ankylosing Spondylitis [26]. It consists of ten questions related to activities of daily living (eight on physical functioning and two on coping with everyday life), which are all scored on a 11-point scale ranging from 0 (easy) to 10 (impossible to perform) with higher scores indicating worse physical functioning. The mean of the individual scores is calculated to give the overall BASFI score ranging from 0 (no impairment) to 10 (severe impairment), with higher scores indicating more functional limitations [26]. A Dutch translation of the BASFI was used.

Patient specific complaints instrument (PSC)

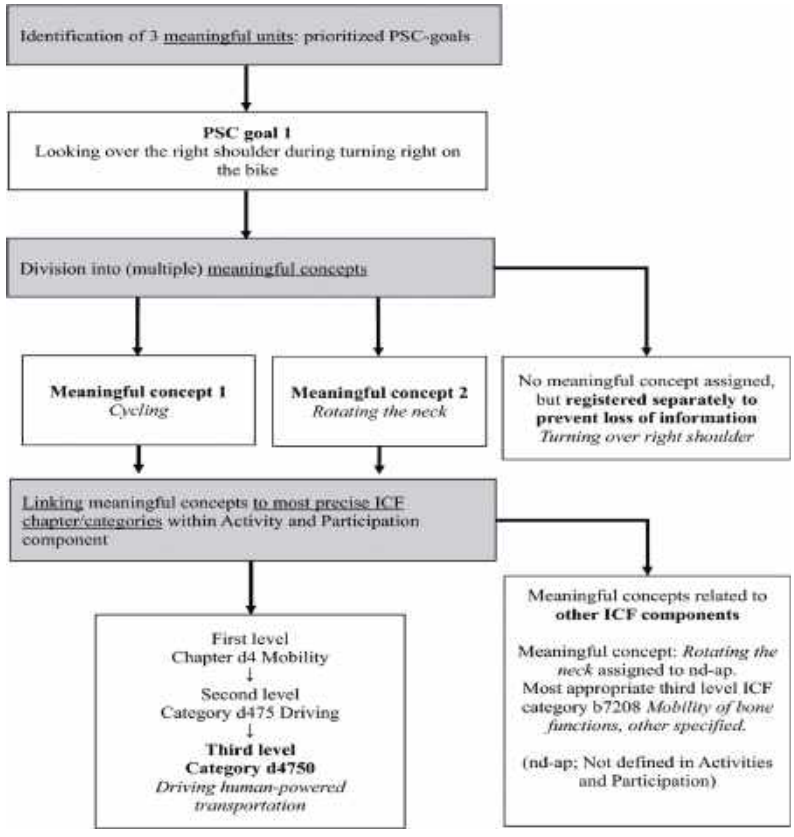
The PSC is a validated instrument in people with chronic diseases to identify and quantify limitations in activity [16-18]. It was administered face-to-face by a trained researcher (MvW, MT). Patients were asked to describe three activities in daily life that were currently difficult to perform and found important to improve. Thereafter, the three PSC activities were prioritized by the patients from most important to least important. Subsequently, the patient was asked to score each of the activities on an 11-point numeric rating scale (NRS) (Anchor 0: able to perform activity without any problems; 10: unable to perform activity). As half of the participants would be randomized to a control condition, participants were not asked to formulate the limited activity in terms of a treatment goal, but only in terms of limited activities they desired to improve.

ICF linking method

The PSC activities were linked to the ICF following standardized linking rules [32, 33]. The linking process is shown in Fig. 1. Prior to the linking process, the researchers individually acquired knowledge of the conceptual fundamental elements of the ICF, components, chapters, categories of the detailed level classification, and definitions. Since the PSC pertains to daily activities, the linking was only done for the ICF component "Activities and Participation". The Dutch translation of the ICF as published on the WHO website was used for the linking process (https://www.whofic.nl/ familie-van-internationale-classificaties /referentie-classificaties / icf accessed 1 November 2022). In addition to the standardized linking rules proposed by Cieza et al. [32, 33], five practical agreements were formulated to facilitate unambiguous definition of concepts and linking to ICF, which are shown in the Supplemental material. Two researchers (MT and TD) independently performed all steps of the linking process. In case of disagreements between the two researchers, a third

researcher (SvW) was consulted. In the first step, each PSC activity was divided into (multiple) relevant meaningful concepts. For example, the PSC activity: "Walking about 3000 m to the supermarket to shop groceries" was divided into two meaningful concepts: "Walking long distances" and "Shopping". Parts of the PSC activity that could not be assigned to a meaningful concept were registered separately to prevent a loss of information. Subsequently, all identified meaningful concepts were linked to the most specific ICF category within the "Activities and Participation" component, with the first level and, where applicable, the second-level category and the third-level category representing increasingly more specific information. For example, the meaningful concept "Cycling" was linked within the first-level category (chapter) "Mobility" and the second-level category "Driving" and to the third-level category "Driving human-powered transportation".

Figure 1 Standardized linking process of the patient specific complaints (PSC) activities to specific International Classification of Functioning, Disability and Health (ICF) categories: an example.



For the determination of the overlap with ICF Core sets, a comparison with the categories in the component "Activities and Participation" of the ICF Core Set for RA [12] and ICF Core Set for Ankylosing Spondylitis (AS) [34] was made. The ICF categories in the ICF RA and AS Core Sets are all defined at the second level. To enable a comparison between the content of the identified PSC activities and the content of the Core Sets, for the activities with a third-level ICF category, the corresponding second-level categories were used. If no ICF category was appropriate within the "Activities and Participation" component but rather another component of the ICF, this meaningful concept was assigned as "not defined in Activities and participation (nd-ap)". For example, if a PSC activity was "Looking over the shoulder when changing direction while riding a bicycle", the meaningful concept "Rotating the neck" was linked to the category nd-ap since the most appropriate ICF category was "Mobility of bone functions, specified".

Analyses

For this analysis, we utilized baseline data from the included patients available on February 14, 2022. As of that date, the inclusion of participants in the studies was still ongoing. The target enrollment for both RCTs was set at 215 participants. Given the descriptive design of this study, in which we wanted to describe the nature of functional limitations no supplementary power calculations were performed. A minimum number of 150 patients per diagnosis group was considered sufficient to estimate both low and high frequencies of specific limitations with sufficient precision. We included all available data at the moment of the analysis as we considered it unethical to leave individuals out [35]. Descriptive analyses of the baseline characteristics were done for people with RA or axSpA separately.

For both populations, the total numbers of meaningful concepts and the numbers and frequencies of unique ICF categories were calculated in total and for each of the three ranked PSC activities separately. In addition, the mean number of ICF categories per PSC activity per participant were calculated. Finally, the overlap with the Comprehensive and Brief ICF Core Sets for RA and AS was determined by comparing the Core Set items to the uniquely identified second-level ICF categories derived from the PSC activities. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), Released 2017, IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, United States of America: IBM Corp.

Results

Demographics and disease characteristics

Table 1 shows the baseline characteristics of the 206 and 155 participants with RA or axSpA with all of the data being normally distributed. Their mean ages (SD) were 58.7 (12.9) and 53.2 (11.8) years), the proportion of females was 90.8% and 47.1% and the self-reported symptom duration was 21.6 (13.5) and 24.7 (14.4) years) in the RA and axSpA groups, respectively. More than 70% of both RA and axSpA groups had three or more comorbidities.

Number of identified meaningful concepts derived from PSC, and total and unique ICF categories

Results are shown in Table 2. In total 911 and 769 meaningful concepts were identified from the PSC activities for people with RA and axSpA, respectively. These were linked to 909 and 759 ICF categories, of which 72 and 57 were unique in RA and axSpA, respectively. All uniquely identified ICF categories were on the second-level (n = 5 in RA and n = 4 in axSpA) or third-level (n = 67 in RA and n = 53 in axSpA). When all meaningful concepts were only linked to second-level categories, there were 25 and 23 unique ICF categories for RA and axSpA, respectively. There were two meaningful concepts in RA and ten in axSpA that could not be linked to an ICF category within the component "Activities and Participation" but within the component "Body functions" and were thus assigned to the "nc-ap" category.

Type and frequency of ICF categories

The total numbers of identified ICF categories in the component "Activities and Participation" and their frequencies are shown in Table 3. Regarding the distribution of the linked activities across the relevant ICF chapters, the majority of the total number of ICF categories related to the ICF chapter "Mobility", in both RA (76.6%) and axSpA (70.1%). None of the activities appeared to be related to the ICF chapters "Learning and applying knowledge", "General tasks or demands" or "Interpersonal interactions and relationships". Table 4 summarizes the five most frequently identified ICF categories based on the meaningful concepts of all three PSC activities combined and per PSC activity separately. For all PSC activities combined, the five most frequent activities related to "Walking" (RA and axSpA both 2: "Walking long distances" and "Walking on different surfaces"), "Changing basic body position (sitting (RA) and bending" (axSpA)), "Stair climbing" (RA), "Grasping" (RA), "Maintaining a standing position" (axSpA), and "Lifting" (axSpA).

Table 1 Baseline characteristics of people with RA or axSpA and severe functional disability participating in a randomized controlled trial on longstanding exercise therapy.

	RA (N=206)	axSpA (N=155)
Age, mean (SD)	58.7 (12.9)	53.2 (11.8)
Sex, female, N (%)	187 (90.8)	73 (47.1)
BMI, mean (SD)	27.6 (6.1)	28.8 (6.6)
Current Medication use, N (%)		
Any DMARD	139 (67.5)	101 (65.2)
csDMARD	83 (59.7)	20 (19.8)
bDMARD	102 (73.4)	93 (92.1)
tsDMARDs	12 (8.6)	0 (0)
NSAIDs	90 (43.7)	79 (51.0)
No antirheumatic or anti-inflammatory medication	9 (4.4)	0 (0)
Self-reported symptom duration (years), mean (SD)	21.6 (13.5)	24.7 (14.4)
Number of comorbidities, N (%)	N=204	N=153
0	7 (3.4)	7 (4.5)
1-2	51 (24.8)	33 (19.3)
3-4	67 (32.5)	46 (29.7)
≥5	79 (38.3)	67 (45.2)
Joint replacement surgeries ≥1, N(%)	80 (38.8)	25 (16.1) N=154
DAS-28, mean (sd)	3.1 (1.3) N=151	-
BASDAI, mean (sd)	-	5.0 (2.0) N=94
Education level, N (%)		
Low	89 (43.2)	39 (25.2)
Medium	58 (28.2)	58 (37.4)
High	59 (28.6)	58 (37.4)
Work status, N (%)		
≤66 years old	147 (71.4)	135 (87.1)
Paid job	42 (28.6)	43 (31.9)
No job, health problems	59 (40.1)	62 (45.9)
No job, other reasons	46 (31.3)	30 (22.2)
PROMIS PF-10 (13.5-61.9), mean (SD)	33.9 (5.2)	35.8 (4.5)
HAQ-DI (0–3), mean (SD)	1.7 (0.5)	-
BASFI (0-10), mean (SD)	-	6.1 (1.9) N=153

axSpA axial spondyloarthritis; BASDAI Bath Ankylosing Spondylitis Disease Activity Index; BASFI Bath Ankylosing Spondylitis Functional Index; bDMARDs biologic disease-modifying anti-rheumatic drugs; BMI Body Mass Index; csDMARDs conventional synthetic disease-modifying anti-rheumatic drugs; DAS-28 Disease Activity Score 28; Education level (Low, primary school or pre-vocational secondary education; Medium, senior general secondary education or pre-university education or secondary vocational education; High, Bachelor or Master at University (of Applied Sciences)); HAQ-DI Health Assessment Questionnaire Disability Index; NSAIDs Nonsteroidal anti-inflammatory drugs; PROMIS PF-10 Patient-Reported Outcomes Measurement Information System Physical Function 10; RA rheumatoid arthritis; tsDMARDs targeted synthetic disease-modifying anti-rheumatic drugs.

Table 2 Results of PSC activities, meaningful concepts and ICF categories in people with RA or axSpA and severe functional disability.

	RA (N=206)	axSpA (N=155)
Total PSC activities, N	618	465
PSC scores (0-10), mean (SD)		
PSC activity 1	7.5 (1.4)	7.8 (1.0)
PSC activity 2	7.5 (1.3)	7.6 (1.1)
PSC activity 3	7.6 (1.3)	7.4 (1.1)
Total meaningful concepts	911	769
Total meaningful concepts "nd-ap"	2	10
Total number of ICF categories	909	759
Total unique ICF categories, second level	5	4
Total unique ICF categories, third level	67	53
ICF categories per participant, mean (SD)	4.4 (0.6)	4.9 (0.8)
ICF categories per participant: 3	42	16
ICF categories per participant: 4	80	44
ICF categories per participant: 5	51	49
ICF categories per participant: 6	24	34
ICF categories per participant: 7	8	9
ICF categories per participant: 8	1	2
ICF categories per participant: 9	-	1

axSpA axial spondyloarthritis; ICF International Classification of Functioning, Disability and Health; IQR interquartile range; PSC patient specific complaints instrument; RA rheumatoid arthritis.

The five most common ICF categories identified based on the separate PSC activities, showed a high agreement, but additionally identified "Driving human-powered transportation" (RA and axSpA), "Manipulating" (RA), "Walking short distances" (RA), "Shopping" (axSpA), "Grasping" (axSpA), "Maintaining a sitting position" (axSpA), and "Changing basic body position: sitting" (axSpA).

When comparing the frequencies of ICF categories across the three ranked activities, limitations in "Walking" were relatively more frequent in the PSC activities ranked 1, in both RA and axSpA. In RA "Changes in basic body position: sitting", "Grasping", and 'Manipulating" were relatively more frequent in activities ranked 2 or 3, whereas in axSpA "Changing basic body position: sitting", "Changing basic body position: bending" and "Lifting" were relatively more frequent in activities ranked 2 or 3.

Table 3 ICF categories in the component "Activities and Participation" derived from PSC activities in people with RA or axSpA and severe functional disability.

Code and description of ICF category	RA (N=206)	axSpA (N=155)
d1 Learning and applying knowledge, N (%)	**0** (0%)	**0** (0%)
➢ *d170 Writing*	*0*	*0*
d2 General tasks and demands, N (%)	**0** (0%)	**0** (0%)
➢ *d230 Carrying out daily routine*	*0*	*0*
➢ *d240 Handling stress and other psychological demands*	*0*	*0*
d3 Communication, N (%)	**6** (0.7%)	**4** (0.5%)
➢ *d345 writing messages*	*3*	*1*
➢ *d360 Using communication devices and techniques*	*3*	*3*
• d3601 Using writing machines	3	3
d4 Mobility, N (%)	**696** (76.6%)	**532** (70.1%)
➢ *d410 Changing basic body position*	*102*	*91*
• d4100 Lying down	2	6
• d4101 Squatting	3	6
• d4102 Kneeling	0	2
• d4103 Sitting	60	30
• d4104 Standing	3	2
• d4105 Bending	22	44
• d4107 Rolling Over	4	0
• d4108 Other specified	8	1
➢ *d415 Maintaining a body position*	*35*	*89*
• d4150 Maintaining a lying position	1	2
• d4151 Maintaining a squatting position	1	0
• d4152 Maintaining a kneeling position	0	1
• d4153 Maintaining a sitting position	10	26
• d4154 Maintaining a standing position	23	60
➢ *d430 Lifting and carrying objects*	*47*	*51*
• d4300 Lifting	34	42
• d4301 Carrying in the hands	7	9
• d4302 Carrying in the arms	6	0
➢ *d435 Moving objects with lower extremities*	*1*	*0*
• d4351 Kicking	1	0
➢ *d440 Fine hand use*	*98*	*62*
• d4400 Picking up	2	4
• d4401 Grasping	51	39
• d4402 Manipulating	44	11
• d4408 Other specified	1	8
➢ *d445 Hand and arm use*	*23*	*10*
• d4452 Reaching	2	6
• d4453 Turning or twisting the hands or arms	11	4
• d4454 Throwing	2	0
• d4455 Catching	1	0
• d4458 Other specified	1	0
• d4459 Unspecified	6	0

Table 3 (continued) ICF categories in the component "Activities and Participation" derived from PSC activities in people with RA or axSpA and severe functional disability.

Code and description of ICF category	RA (N=206)	axSpA (N=155)
➢ *d449 Carrying, moving, and handling objects, other specified and unspecified*[a]	*0*	*0*
➢ *d450 Walking*	*268*	*158*
• d4500 Walking short distances	48	12
• d4501 Walking long distances	121	92
• d4502 Walking on different surfaces	79	43
• d4508 Other specified	20	11
➢ *d451 Stair climbing*	*62*	*32*
➢ *d455 Moving around*	*3*	*2*
• d4451 Climbing	0	1
• d4552 Running	1	0
• d4554 Swimming	2	1
➢ *d460 Moving around in different locations*	*7*	*2*
• d4600 Within the home	2	2
• d4602 Outside the home and other buildings	1	0
• d4608 Other specified	4	0
➢ *d465 Moving around using equipment*	*0*	*0*
➢ *d470 Using transportation*	*0*	*0*
➢ *d475 Driving*	*50*	*35*
• d4750 Driving human-powered transportation	37	25
• d4751 Driving motorized vehicles	3	4
• d4752 Driving animal-powered vehicles	1	0
• d4758 Other specified	9	6
d5 Self-care, N (%)	**69** (7.6%)	**60** (7.9%)
➢ *d510 Washing oneself*	*22*	*9*
d5100 Washing body parts	5	3
d5101 Washing whole body	9	4
d5102 Drying oneself	8	2
➢ *d520 Caring for body parts*	*2*	*2*
d5202 Caring for hair	1	2
d5204 Caring for toenails	1	0
➢ *d530 Toileting*[a]	*7*	*7*
d5301 Regulating defecation	4	4
➢ *d540 Dressing*	*35*	*42*
d5400 Putting on clothes	22	21
d5401 Taking off clothes	7	2
d5402 Putting on footwear	6	19
➢ *d550 Eating*	*3*	*0*
➢ *d560 Drinking*	*0*	*0*
➢ *d570 Looking after one's health*	*0*	*0*

Table 3 (continued) ICF categories in the component "Activities and Participation" derived from PSC activities in people with RA or axSpA and severe functional disability.

Code and description of ICF category	RA (N=206)	axSpA (N=155)
d6 Domestic life, N (%)	**100** (11.0%)	**136** (17.9%)
➢ *d620 Acquisition of goods and services*	*19*	*35*
• d6200 Shopping	19	35
➢ *d630 Preparing meals*	*23*	*32*
• d6300 Preparing simple meals	4	2
• d6309 Preparing meals, unspecified	19	30
• d6403 Using household appliances	29	28
➢ *d640 Doing housework*	*38*	*44*
• d6400 Washing and drying clothes and garments	1	2
• d6401 Cleaning cooking area and utensils	0	3
• d6402 Cleaning living area	6	7
• d6403 Using household appliances	29	28
• d6408 Other specified	1	4
• d6409 Unspecified	1	0
➢ *d650 Caring for household objects*	*19*	*23*
• d6501 Maintaining dwelling and furnishings	0	1
• d6503 Maintaining vehicles	2	0
• d6505 Taking care of plants, indoors and outdoors	11	17
• d6506 Taking care of animals	6	5
➢ *d660 Assisting others*	*1*	*2*
• d6609 Assisting others, unspecified	1	2
d7 Interpersonal interactions and relationships, N (%)	**0** (0%)	**0** (0%)
➢ *d760 Family relationships*	*0*	*0*
➢ *d770 Intimate relationships*	*0*	*0*
d8 Major life areas, N (%)	**3** (0.3%)	**4** (0.5%)
➢ *d845 Acquiring, keeping, and terminating a job*	*0*	*0*
➢ *d850 Remunerative employment*	*0*	*0*
➢ *d859 Work and employment, other specified and unspecified*	*3*	*4*
➢ *d870 Economic self-sufficiency*	*0*	*0*
d9 Community, social and civic life, N (%)	**36** (4.0%)	**23** (3.0%)
➢ *d910 Community life*	*0*	*0*
➢ *d920 Recreation and leisure*	*36*	*23*
d9200 Play	1	0
d9201 Sports	8	3
d9202 Arts and culture	8	0
d9203 Crafts	1	0
d9205 Socializing	5	5
d9208 Other specified	3	0
d9209 Unspecified	10	15

axSpA axial spondyloarthritis; ICF International Classification of Functioning, Disability and Health; PSC patient specific complaints instrument; RA rheumatoid arthritis.

[a] The ICF category for d530 toiling comprised a total 7 for RA and for axSpA. Four times for both RA and axSpA the ICF category d4531 was assigned and 3 times for both RA and axSpA d530 was assigned.

Table 4 Five most prevalent ICF categories identified in people with RA or axSpA and severe functional disability, in total and by PSC activity.

RA (N=206)			
Ranking	**ICF Code**	**Total three PSC Activities (N=909 ICF categories)**	**Number of ICF categories (%)**
1	d4501	Walking long distances	121 (13.3)
2	d4502	Walking on different surfaces	79 (8.7)
3	d451	Stair climbing	62 (6.8)
4	d4103	Changing basic body position: sitting	60 (6.6)
5	d4401	Grasping	51 (5.6)
Ranking	**ICF Code**	**PSC Activity 1 (N=316 ICF categories)**	**Number of ICF categories (%)**
1	d4501	Walking long distances	75 (23.7)
2	d4502	Walking on different surfaces	47 (14.9)
3	d4500	Walking short distances	33 (10.4)
4	d4401	Grasping	14 (4.4)
5	d4103	Changing basic body position: sitting	12 (3.8)
Ranking	**ICF Code**	**PSC Activity 2 (N=294 ICF categories)**	**Number of ICF categories (%)**
1	d4501	Walking long distances	28 (9.5)
2	d451	Stair climbing	25 (8.5)
3	d4103	Changing basic body position: sitting	20 (6.8)
4	d4750	Driving human-powered transportation	19 (6.4)
5	d4401	Grasping	18 (6.1)
Ranking	**ICF Code**	**PSC Activity 3 (N=299 ICF categories)**	**Number of ICF categories (%)**
1	d4103	Changing basic body position: sitting	28 (9.4)
2	d451	Stair climbing	27 (9.0)
3	d4402	Manipulating	20 (6.7)
4	d4401	Grasping	19 (6.4)
5	d4501	Walking long distances	18 (6.0)

Table 4 (continued) Five most prevalent ICF categories identified in people with RA or axSpA and severe functional disability, in total and by PSC activity.

AxSpA (N=155)			
Ranking	**ICF Code**	**Total three PSC Activities (N=759 ICF categories)**	**Number of ICF categories (%)**
1	d4501	Walking long distances	92 (12.1)
2	d4154	Maintaining a standing position	60 (7.9)
3	d4105	Changing basic body position: bending	44 (5.8)
4	d4502	Walking on different surfaces	43 (5.7)
5	d4300	Lifting	42 (5.5)
Ranking	**ICF Code**	**PSC Activities 1 (N=247 ICF categories)**	**Number of ICF categories (%)**
1	d4501	Walking long distances	50 (20.2)
2	d4502	Walking on different surfaces	22 (8.9)
3[a]	d4154 /	Maintaining a standing position /	17 (6.9)
	d451	Stair climbing	17 (6.9)
5[a]	d4300 /	Lifting /	10 (4.0)
	d4153	Maintaining a sitting position	10 (4.0)
Ranking	**ICF Code**	**PSC Activities 2 (N=253 ICF categories)**	**Number of ICF categories (%)**
1	d4154	Maintaining a standing position	30 (11.9)
2[a]	d4105 /	Changing basic body position: bending	19 (7.5)
	d4501	Walking long distances	19 (7.5)
4	d4401	Grasping	16 (6.3)
5	d4750	Driving human-powered transportation	14 (5.5)
Ranking	**ICF Code**	**PSC Activities 3 (N=259 ICF categories)**	**Number of ICF categories (%)**
1	d4501	Walking long distances	23 (8.9)
2	d4300	Lifting	20 (7.7)
3[a]	d6200 /	Shopping	16 (6.2)
	d4105	Changing basic body position: bending	16 (6.2)
5	d4103	Changing basic body position: sitting	15 (5.8)

axSpA axial spondyloarthritis; ICF International Classification of Functioning, Disability and Health; PSC patient specific complaints instrument; RA rheumatoid arthritis.
[a] Shared ranking in top-5 due to same reported number.

Overlap and differences between identified ICF categories and the Brief and Comprehensive ICF Core Sets

An overview of the overlap and differences between the identified ICF categories and the Comprehensive and Brief ICF Core Sets for RA and axSpA within the "Activities and Participation" component is presented in Table 5. The Comprehensive Core Set for RA consists of 32 second-level categories of which 21 (66%) were present in this study. The Brief Core Set for RA consists of six items of which four (67%) were present in this study. Of the 25 identified second-level ICF categories in our study, four categories were not included in the Core Sets for RA: "Stair climbing", "Writing messages", "Moving objects with lower extremities", and "Caring for household objects" with "Stair climbing" being the most common (62/909 total number of ICF categories, 6.8%).

The Comprehensive Core Set for AS comprises of 24 second-level categories of which 14 were reported in this study (58%). The Brief Core Set for AS consists of eight items of which four (50%) were present in this study. Of the 23 identified second-level categories, nine categories were not included in the Core Sets for AS: "Fine hand use", "Writing messages", "Using communication devices and techniques", "Hand and arm use", "Moving around in different locations", "Preparing meals", "Caring for household objects", "Work and employment, other specified and unspecified", and "Stair climbing" with "Fine hand use" being most frequent (62/759 total number of ICF categories, 8.2%).

Table 5 ICF Core Sets categories in the component "Activities and Participation" and their overlap with the ICF categories derived from PSC activities in people with RA or axSpA and severe functional disability.

ICF category	RA (N=206)	ICF Core Sets RA	axSpA (N=155)	ICF Core Sets AS
d170 Writing	-	*	-	
d230 Carrying out daily routine	-	**	-	**
d240 Handling stress and other psychological demands	-		-	*
d345 Writing messages	+		+	
d360 Using communication devices and techniques	+	*	+	
d410 Changing basic body position	+	**	+	**
d415 Maintaining a body position	+	*	+	*
d430 Lifting and carrying objects	+	*	+	*
d435 Moving objects with lower extremities	+		-	
d440 Fine hand use	+	**	+	
d445 Hand and arm use	+	**	+	
d449 Carrying, moving, and handling objects, other specified and unspecified	-	*	-	
d450 Walking	+	**	+	**
d451 Stair climbing	+		+	
d455 Moving around	+	*	+	*
d460 Moving around in different locations	+	*	+	
d465 Moving around using equipment	-	*	-	
d470 Using transportation	-	*	-	*
d475 Driving	+	*	+	**
d510 Washing oneself	+	*	+	*
d520 Caring for body parts	+	*	+	*
d530 Toileting	+	*	+	*
d540 Dressing	+	*	+	*
d550 Eating	+	*	-	
d560 Drinking	-	*	-	
d570 Looking after one's health	-	*	-	*
d620 Acquisition of goods and services	+	*	+	*
d630 Preparing meals	+	*	+	
d640 Doing housework	+	*	+	*
d650 Caring for household objects	+		+	
d660 Assisting others	+	*	+	*
d760 Family relationships	-	*	-	**
d770 Intimate relationships	-	*	-	*
d845 Acquiring, keeping, and terminating a job	-		-	**
d850 Remunerative employment	-	**	-	**
d859 Work and employment, other specified and unspecified	+	*	+	
d870 Economic self-sufficiency	-		-	*
d910 Community life	-	*	-	*
d920 Recreation and leisure	+	*	+	**
ICF Categories in Comprehensive ICF Core Set		32		24
Total number of second-level ICF categories	25		23	
Overlapping ICF categories with Comprehensive Core Set	21		14	
ICF categories in Brief ICF Core Set		6		8
Overlapping ICF categories with Brief Core Set	4		4	

AS ankylosing spondylitis; axSpA axial spondyloarthritis; ICF International Classification of Functioning, Disability and Health; RA rheumatoid arthritis.
- Not included in our study population.
+ Included in our study population.
* Included in the Comprehensive Core Set.
** Included in the Brief and Comprehensive Core Set.

Discussion

The most frequent limitations in activities as prioritized by people with RA or axSpA and severe functional disability concerned the ICF chapter "Mobility", in particular the categories related to "Walking" and "Changing basic body position". In RA, other frequent limitations were related to "Grasping" and "Stair climbing" whereas in axSpA this concerned "Lifting" and "Maintaining a standing position". There was considerable overlap between the ICF categories identified in the study populations and the corresponding ICF Core Sets, to a greater extent in RA than in axSpA. In our study population, thirteen ICF categories (four in RA and nine in axSpA) were identified that were not included in the Comprehensive Core Sets for RA/AS. Among these categories, "Stair climbing" for RA and "Fine hand use" for axSpA demonstrated a prevalence of more than 5%.

Our findings are partly in line with a previous study employed in four different countries linking rehabilitation goals to the ICF in people with RA patients, where within the "Activities and Participation" component "Walking" and "Self-care" reported most [10]. Activities such as "Stair climbing" and "Changing basic body position" were frequently reported in our population but were not found in the latter study. The previous study did not include patients with axSpA, whereas the inclusion of two populations within our study enabled the comparison among people with different rheumatological diagnoses.

Other comparisons are difficult to make, as the population, setting and methods in the present study importantly differed from the previous study [10]. In the present study, the included participants had more functional disability as shown by higher HAQ-DI scores, and were treated in primary care and not in a multidisciplinary rehabilitation setting. Moreover, a different method for the assessment of treatment goals was used with elicitation and prioritization of limited activities without explicit goal-setting and only pertained to one component of the ICF (i.e. "Activities and Participation"). Our study also included people with axSpA, in which knowledge on this topic is more limited. A study in veterans with spondyloarthritis (SpA, including AS) explored the relation between the disease and physical function [36] by means of a survey. They found veterans with SpA had significant more limitations in "Walking", "Transferring", and "Dressing" [36]. Although, this study did not use treatment goals, the findings are similar to our study.

The content of the Brief and Comprehensive Core Sets for RA or AS were well reflected in the prioritized activities. Overall, more than half of linked ICF categories as derived from the prioritized limited activities corresponded with the contents of the ICF Core Sets for RA or AS. However, there were exceptions in our study, where certain categories such as "Carrying out daily routine", "Remunerative employment", "Family relationships", and "Acquiring, keeping, and terminating a job" were included in the Brief and Comprehensive Core Sets for AS but were not identified in our study populations. Similarly, for RA, the ICF categories "Carrying out daily routine" and "Remunerative employment" were part of the Brief and Comprehensive Core Sets for RA but were not identified in our study populations. A possible reason for the absence of these categories in our populations could be due to participants being requested to identify three specific limitations in activities that were found important and could be improved with an intervention such as exercise therapy. The discrepancies between the nature of limited activities seen in the present study and the content of the corresponding ICF Core Sets may warrant further exploration. It is first of all possibly related to the specific selection of the study population, being a population of people with severe functional disability. Moreover, the ICF Core Sets were developed more than 10 years ago (RA in 2004 and AS in 2010). Due to the developments of pharmacological interventions in recent years and changing needs of society, limitations in activity might also have evolved over time. Furthermore, for people with axSpA, only the ICF Core Sets for AS were available, whereas the axSpA population encompasses both radiographic and non-radiographic axSpA with patients possibly facing other challenges in daily activities.

This study has a number of limitations. First, as our study concerned baseline data of RCTs with specific inclusion and exclusion criteria, it thus concerns a selected population. Moreover, as our RCTs pertained to long standing exercise therapy, patients with a relatively positive attitude towards exercise therapy may have been overrepresented. Either or not related to the previous points, the proportion of females was relatively high in our population, whereas it is known that women are in general more willing to participate in research than men [37]. Second, this study concerned the ICF component "Activities and Participation" only and we can, therefore, not make assumptions on limitations perceived regarding the other ICF components. Finally, despite the elaborate descriptions of the methods for linking goals to the ICF as proposed by Cieza et al. [32, 33], it was in some cases challenging to link free text of PSC activities to the most appropriate ICF category. For

example, PSC activities did not always contain enough specific information to determine the most precise category resulting in the ICF category unspecified. Accurately setting treatment goals can be challenging, because it refers to a future state of functioning achieved through planned treatment actions. A PSC activity that does not contain enough information to determine the most precise ICF category highlights the need for more training of healthcare professionals on goal-setting to further improve the use of PSC activities for individualized tailored treatment of people with RA or axSpA. To overcome some of these problems, some adaptions or additions to the existing linking rules may facilitate unambiguous definition of meaningful concepts and linking to the ICF.

In conclusion, to our knowledge, this is the first study describing the nature of functional limitations as assessed with the PSC for people with RA or axSpA and severe functional disability. It provides insight into the nature and most frequent functional limitations in this subgroup within the "Activities and Participation" component of the ICF, and can, therefore, facilitate healthcare professionals in identifying individual functional limitations in activities and participation and thus improving treatment. The overlap with the Core Sets for RA and AS was relatively high, however, clinicians should be aware that not all RA or AS Core Sets items are prevalent in practice and some prevalent activity limitations prioritized by individual patients are not included in the ICF Core Sets.

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Author contributions

All authors made substantial contributions to the conception or design of the study or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work. MMHT, TD, SFEW and TPMVV contributed substantially to the analysis and interpretation of data. Furthermore, all authors were involved in drafting the work or revising it critically for important intellectual content, and approved the version to be published. Finally, all authors agreed to be accountable for appropriate portions for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare that they have no known conflicts of interest.

Supplementary files

- Supplementary file 1: STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies.

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Supplemental files

Supplementary file 1 STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies.

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Title page
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4/5*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N.A.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	N.A.
		(*c*) Explain how missing data were addressed	N.A.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	N.A.

Supplementary file 1 (continued) STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies.

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	N.A.
		(c) Consider use of a flow diagram	N.A.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	8/9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N.A.
		(*b*) Report category boundaries when continuous variables were categorized	N.A.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N.A.

Discussion

Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page

6

Chapter 6

Extent and nature of functional limitations according to the Health Assessment Questionnaire Disability Index in patients with Rheumatoid Arthritis and severe functional disability study

Max M. H. Teuwen[1], Maria A. T. van Wissen[1], Wilfred F. Peter[1], Dirkjan van Schaardenburg[2], Cornelia H. M. van den Ende[3,4], Maaike G. J. Gademan[1,5], Salima F. E. van Weely[1]

1. Department of Orthopaedics, Rehabilitation and Physical Therapy, Leiden University Medical Center, Leiden, The Netherlands;
2. Center for Rehabilitation and Rheumatology, Reade, Amsterdam, The Netherlands;
3. Department of Rheumatology, Radboud UMC, Nijmegen, The Netherlands;
4. Department of Research, Sint Maartenskliniek, Nijmegen, The Netherlands;
5. Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.

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Abstract

Background: For a subgroup of people with rheumatoid arthritis (RA) and severe disability, insight into their limitations is crucial for adequate treatment. Aim: To describe the extent and nature of functional limitations in people with RA and severe disability and to explore the associations of the extent of the functional limitations with patient characteristics, disease characteristics, and outcome measures.

Methods: Baseline data of 215 participants in an RCT on the (cost-)effectiveness of longstanding physiotherapy were used. Functional limitations were assessed with the Health Assessment Questionnaire Disability Index (HAQ-DI). The total HAQ-DI including eight domain scores were calculated. Associations between high HAQ-DI scores (≥2, yes/no) and other variables were examined using the Student's t-test or Chi-squared test where appropriate.

Results: The participants (90% women, age 58.8 ± 12.8 years) had a mean HAQ-DI score of 1.7 ± 0.5. The majority (56%) showed a moderate-to-severe disability in all domains. Higher HAQ-DI scores seemed to be associated with advanced age, longer disease duration, unemployment, joint replacements, and outcomes for daily functioning and physical quality of life, but not with measures of disease activity.

Conclusion: Our findings indicate that a comprehensive assessment of all areas of daily activities in this subgroup is necessary in order to provide appropriate (non-) pharmacological care.

Keywords: Rheumatoid arthritis; Functional disability; HAQ-DI; Rehabilitation; Patient-reported outcomes

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that causes inflammation and the progressive destruction of the joints affecting approximately 0.5–1% of the general population [1–3]. It can lead to pain, fatigue, and functional disability with a considerable impact on quality of life (QoL) [3–5]. Pharmacological treatment options have greatly improved in recent decades, leading to an overall better level of functioning and QoL [6]. Despite the availability of these effective treatments, there is a subgroup of people with RA who have considerable functional limitations due to persistently high disease activity and a proportion of people in this subgroup may be classified as difficult-to-treat RA (D2T) [7, 8]. Moreover, existing joint destruction, deformities, or the presence of comorbidities can also contribute to functional disability [9]. This can affect people's ability to perform even simple everyday activities [10–13] and may mean that they require support with non-pharmacological treatment modalities such as physiotherapy, occupational therapy, or rehabilitation [8, 14]. More insight into both the extent and nature of the functional disability is important to provide adequate treatment that meets the (therapeutic) needs of this specific subgroup and direct (non-)pharmacological interventions to the right domains thereby improving the disability and QoL.

To our knowledge, there is a paucity of studies examining the nature of functional disability in general and especially in the subgroup of people with RA and severe disability. One study assessed the limitations in physical functioning in people with RA eligible for rehabilitation treatment and thus likely to have considerable disability [15]. In that study, executed in four countries, the content of rehabilitation treatment goals was analyzed using the International Classification of functioning disability and Health (ICF) as a reference [15]. It was shown that most limitations (44%) were observed in the domain "Activities and Participation", with the top 3 pertaining to "Learning and applying knowledge" (d1), "Mobility" (d4), and "Self-care" (d5) [15]. A recent, comparable study by our research group linked the prioritized functional limitations, as measured with the Patient Specific Complaints instrument (PSC) [16] into ICF categories. For this study, people with RA who participated in a randomized controlled trial (RCT) of long-term exercise therapy were included. From that study, it was concluded that limitations in activities were most frequently seen in "Walking", "Changing basic body position", "Grasping", and "Stair climbing". However, both studies used a method to assess and prioritize personalized treatment goals, rather than a fixed set of activities. This complicates the interpretation and

comparability of problems within groups and between individuals. The most frequently used patient-reported outcome measure to assess functional ability in people with RA in both research and clinical settings is the Health Assessment Questionnaire Disability Index (HAQ-DI) [17, 18]. The HAQ-DI assesses an individual's abilities over the past week using their usual equipment. The HAQ-DI is mainly used to quantify (changes in) the degree of disability severity and focuses on limitations in activities, taking into account some aspects of the patient's physical environment [19]. It was applied and validated in patients with a wide variety of rheumatic diseases, including RA [17, 18]. It is sensitive to change and is a good predictor of future disability [9, 20], sustained remission in the course of RA [21], and provides decision support where there is a need for multidisciplinary interventions [22]. However, these papers lack details on the nature of the limitations and did not specifically report on individuals within the RA population who were experiencing severe functional disability.

Moreover, within the broader RA population, the HAQ-DI exhibits a robust correlation with various measures of physical functioning and QoL, including the Patient-Reported Outcomes Measurement Information System Physical Function 10 (PROMIS PF-10) [23] and the 36-Item Short-Form Health Survey Physical Component Summary Scale (SF-36 PCS) [24].

While functional disability is known to be linked to disease activity [9, 25, 26], it is imperative to recognize that it can also be influenced by other factors such as joint damage, deformities, complications arising from the disease or its treatment, and/or comorbidities [9, 26].

The subgroup of individuals with RA and severe functional disability forms a distinctive cohort, potentially requiring unique support from various healthcare professionals. The absence of exploration into this specific subgroup raises critical questions about the specific challenges they encounter in their daily lives and the potential impact on their overall well-being. Gaining insight into the severity and nature of functional limitations through the HAQ-DI, along with exploring associations with patient or disease characteristics and other questionnaires, could contribute to refining healthcare strategies. This approach aims to foster a more targeted and personalized approach to managing severe functional disability in individuals with RA.

Therefore, the objective of our study was twofold: first, to describe the extent and nature of functional limitations in people with RA using the HAQ-DI, and second, to explore which patient characteristics, disease characteristics, and/or other measures of physical functioning and QoL are associated with a higher HAQ-DI score within this subgroup.

Materials and Methods

Study Design

This is a secondary analysis of baseline data from an RCT comparing the (cost-)effectiveness of longstanding exercise therapy to usual care in people with RA and severe functional disability. A detailed description of the study methods including inclusion and exclusion criteria, assessments, study procedures, and intervention description for this RCT is published elsewhere [27]. The trial was approved by the Medical Ethical Committee Leiden-Den Haag-Delft (METC LDD; L-EXTRA: NL69866.058.19) and registered in the International Clinical Trials Registry Platform (ICTRP): (Longstanding EXercise Therapy in patients with Rheumatoid Arthritis; L-EXTRA; NL8235). The study was conducted in accordance with the principles of the Declaration of Helsinki (2013) [28]. All participants gave written informed consent before entering the study.

Participants

Participants were recruited via various social media channels and 50 rheumatology outpatient departments spread across all provinces of the Netherlands. Adults (aged≥18 years), with a clinical diagnosis of RA made by a rheumatologist and self-perceived severe limitations in functioning involving self-care (e.g., dressing and washing), and/or transfers (e.g., getting in and out of bed, rising from a chair or using the toilet), and/or mobility indoors or outdoors were included. Limitations had to be directly or indirectly related to the rheumatic condition, e.g., caused by persisting or progressive disease activity despite optimal medical treatment and/or severe joint damage and/or deformities and/or severe comorbidity, e.g., pulmonary or cardiovascular disease. Furthermore, it was judged that their functional limitations were unlikely to improve or resolve with a brief exercise therapy intervention, as assessed by two experienced physical therapists involved in the research team.

Assessments

For the current study, we used the following baseline assessments: the baseline questionnaire, which was filled out online by all participants, and the baseline the 6 min walk test (6MWT). The 6MWT was assessed by a researcher (M.M.H.T. or M.A.T.v.W. following a standardized protocol published in the study protocol [27]). Reminders were given by mail and telephone. Disease characteristics were retrieved via the treating rheumatologist. The following characteristics were used: socio-demographics (gender, age, body mass index, single person household, education level, work status (in participants aged ≤66 years), disease characteristics (symptom duration, disease duration, fulfilment of D2T RA criteria [7], rheumatoid factor (RF-positive), anti-citrullinated protein antibodies (ACPA positive), Disease Activity (Disease Activity Score 28 joints, DAS-28) [29, 30], current medication), medical history (smoking status, number of co-morbidities, number of joint replacement surgeries), measures of physical functioning (Patient-Reported Outcome Measurement Information System Physical Function 10-Item Short Form (PROMIS PF-10, range 13.5 to 61.9 with higher scores corresponding with better physical functioning) [31–33], the HAQ-DI [17, 18]), measures of QoL (36-Item Short-Form Health Survey Mental and Physical Component Summary Scale (SF-36 MCS/PCS, range 0–100, worst–best) [34, 35]), measure of performance-based physical functioning (6MWT, distance walked in meters).

HAQ-DI and Functional Disability

The HAQ-DI was used to assess the extent and nature of functional disability [17, 18]. The HAQ-DI reflects problems in activities of daily living and consists of 20 items divided over eight domains (Dressing and grooming, Arising, Eating, Walking, Personal hygiene, Reaching, Gripping and Usual activities). Each item is scored on a 4-point scale ranging from 0 to 3 (0 = without ANY difficulty 1 = with SOME difficulty, 2 = with MUCH difficulty, 3 = UNABLE to do), with the total HAQ-DI score ranging from 0 to 3 (no disability to very severe disability) [36]. To determine the participants' functional disability, domain scores and the total HAQ-DI score were calculated with the correction for the use of assistive devices. The use of aids or devices or physical assistance increases a score of 0 or 1 to a 2 to more accurately represent underlying disability; scores of 3 are not modified. Scores of 0 to 1 generally represent mild-to-moderate difficulty, 1 to 2 represent moderate-to-severe disability, and 2 to 3 indicate severe-to-very-severe disability [17]. A HAQ-DI score of <0.5 is often used in studies to describe normative physical function [5].

Statistical Analyses

The data are presented as mean (standard deviation (SD)) and number and percentage (n, %) as appropriate. To assess the extent of functional disability the HAQ-DI score and domain scores (mean, SD) were calculated. To get more insight into the nature of functional disability within each domain the percentages of participants reporting no/some/much difficulty of inability to perform the activities was calculated and the domain with the highest percentage of participants with a maximum score of 3 was identified. In addition, for each participant, the number of domains with a score ≥ 1 was determined.

To explore potential associations with patient characteristics, disease characteristics, and other baseline questionnaire variables, we categorized patients into two groups based on their HAQ-DI scores, distinguishing between high and lower scores. We arbitrarily established, on the basis of consensus among authors, a cut-off point at a HAQ-DI score < 2 (mild-to-moderate) and a HAQ-DI score ≥ 2 (severe-to-very-severe). Subsequently, we conducted unpaired t-tests (including mean difference and 95% Confidence Interval (CI)) for continuous data, Pearson's Chi-squared tests and calculated the odds ratio (OR) and 95% CI for dichotomous data to assess potential associations. Considering the explorative nature of these analyses we did not perform a formal sample size calculation. Statistical analyses were performed in IBM SPSS Statistics version 25.0 (Released 2017, Armonk, NY, USA: IBM Corp.).

Results

Baseline Characteristics

The baseline characteristics of the study population are summarized in Table 1. In total, data from 215 participants with RA were used who were mainly women (n = 194; 90%) with a mean age of 58.8 (SD ± 12.8) years and a mean disease duration of 18.8 (±13.0) years. Among the working-age participants (n = 154, 72%), the majority were not employed due to health problems (n = 61, 40%). Nearly half of the study population met the D2T RA criteria [7] (n = 90, 47%), and 37% (n = 80) had undergone one or more joint replacement surgeries, and the majority had three or more comorbidities (n = 154/213, 72%). The mean scores for the PROMIS PF-10 (33.9 ± 5.1) and SF-36 PCS scores (29.5 ± 7.8) are indicative of considerable disability.

Table 1 Baseline characteristics of participants with RA and severe disability (n=215).

Female, n (%)	194 (90)
Age in years, mean (SD)	58.8 (12.8)
BMI (kg/m2), mean (SD)	27.6 (6.0)
Single-person household, n (%)	67 (31)
Higher Education, n (%)	62 (29)
Work status, n (%)	
≤66 years old, n (%)	154 (72)
Paid job, n (%)	*45 (29)*
No job, health problems, n (%)	*61 (40)*
No job, other reasons, n (%)	*48 (31)*
Self-reported symptom duration (years), mean (SD)	21.6 (13.3)
Disease duration (years), Mean (SD)	18.8 (13.0) (n=193)
Difficult-to-treat RA criteria[a], n (%)	90 (47) (n=191)
RF positive, n (%)	127 (68) (n=187)
ACPA positive, n (%)	113 (61) (n=184)
DAS-28[b], mean (SD)	3.1 (1.3) (n=159)
Current medication use[c], n (%)	
Any DMARD	149 (69)
bDMARD	114 (77)
tsDMARD	12 (8)
csDMARD	86 (58)
NSAIDs	98 (46)
Glucocorticoids *Oral*	51 (24)
Glucocorticoids *Injection intra-muscular / intra-articular*	31 (14)
No RA treatment related medication	10 (9)
Number of comorbidities, n (%)	(N=213)
0	8 (4)
1-2	51 (24)
3-4	72 (33)
≥5	82 (39)
Joint replacement surgeries ≥1, n (%)	80 (37)
PROMIS PF-10, mean (SD)	33.9 (5.1)
SF-36 MCS, mean (SD)	46.7 (12.4)
SF-36 PCS, mean (SD)	29.5 (7.8)
HAQ-DI mean (SD)	1.7 (0.5)
6MWT distance (meters), mean (SD)	305 (96) (n=213)

ACPA, anti-citrullinated protein antibodies; BMI, Body Mass Index; DAS-28, Disease Activity Score; DMARDs, Disease-Modifying Antirheumatic Drugs; HAQ-DI, Health Assessment Questionnaire Disability Index; Higher education, Bachelor or Master at University (of Applied Sciences); and doctoral degree program at research universities; PROMIS PF-10, Patient Reported Outcomes Measurement Information System Physical Functioning-10; RF, Rheumatoid Factor; bDMARDS, biological Disease-Modifying Antirheumatic Drugs; tsDMARD, targeted synthetic Disease-Modifying Antirheumatic Drugs; csDMARD conventional synthetic Disease-Modifying Antirheumatic Drugs; SF-36 MCS/PCS, 36-Item Short-Form Health Survey Mental/Physical Component Summary Scale; 6MWT, 6-minute walk test.

[a] Difficult-to-treat RA definition based on Nagy et al. [7].

[b] DAS-28 score is based on the ESR and if the DAS-28 score was based on the CRP score the following calculation was used: DAS28-ESR=3.3928*Ln (DAS-28-CRP)+0.0254 [30].

[c] Multiple answers possible.

Extent and Nature of Functional Disability

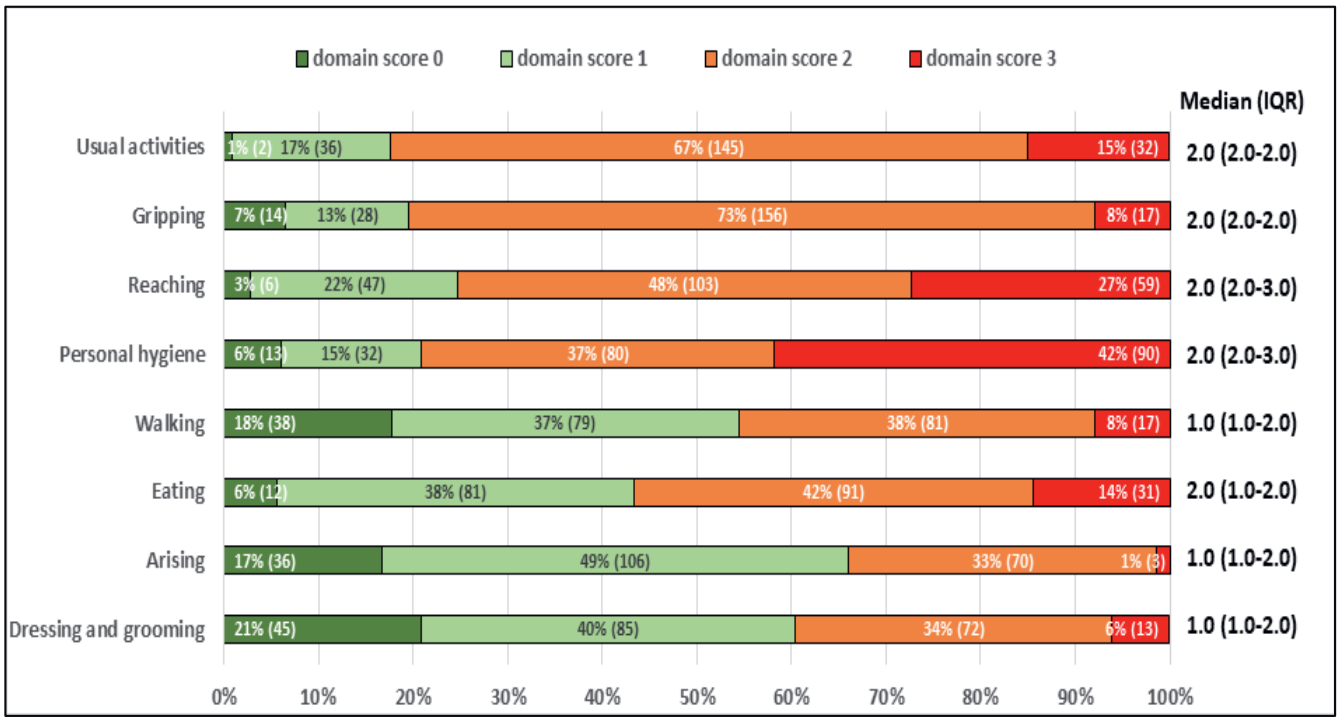
Data showed considerable disability within the study population, as indicated by a mean HAQ-DI score of 1.7 (SD ± 0.5). In addition, the majority (n = 200, 93%) had a HAQ-DI score of ≥1, indicating moderate-to-severe functional disability.

Figure 1 shows the median HAQ-DI domain scores. All median scores were ≥1, ranging from 1.0 to 2.0 with a minimum score of 0 and a maximum score of 3. It also shows the percentage and number of participants with domain scores 0, 1, 2, or 3 for all eight domains. Most severe limitations were observed in the domains of Usual Activities, Gripping, Reaching and Personal hygiene, with 75% or more of the study population showing a domain score of 2 or 3, indicating severe disability. The highest percentage of participants with a domain score of 3 was seen in the domain of Personal hygiene (42%, n = 90).

Regarding the number of domains with a score of ≥1, the frequencies are shown in Figure 2 and the interquartile range was 7–8 (range 3–8). All participants showed to be limited in at least three domains, with the majority of the participants having a domain score ≥1 in all eight (56%, n = 120) or seven domains (23%, n = 50). In addition, 13% (n = 28) showed limitations in six domains and only the minority (n = 17, 8%) in five or fewer domains, indicating that within this population of people with RA, functional disability is present in most domains.

Figure 3 shows the distribution of patients reporting a score of ≥1 (indicating some difficulties or worse) for individual items on the HAQ-DI. While scores varied, most items showed a percentage of at least 53% of patients reporting a score ≥1, barring one exception: “Lift a full cup or glass to your mouth”. Conversely, the most restrictive item, “Do chores such as vacuuming or yard work”, has a notably higher prevalence, with 97% of patients reporting a score of ≥1. For items most frequently reported with a score of 2 or 3 (indicating much difficulty or an inability to perform), three stand out across different domains. In the Usual activities domain, “Do chores such as vacuuming or yard work” is particularly challenging for 56% of patients. In the Reaching domain, “Reach and get down a 5-pound object from above your head” proves to be of substantial difficulty for 63% of patients. Similarly, in the Personal hygiene domain, “Take a tub bath” is notably challenging, with 65% of patients scoring 2 or higher.

Figure 1 The percentages and number of participants with domain scores ranging from 0-3 for each domain and mean HAQ-DI domain score (n=215).



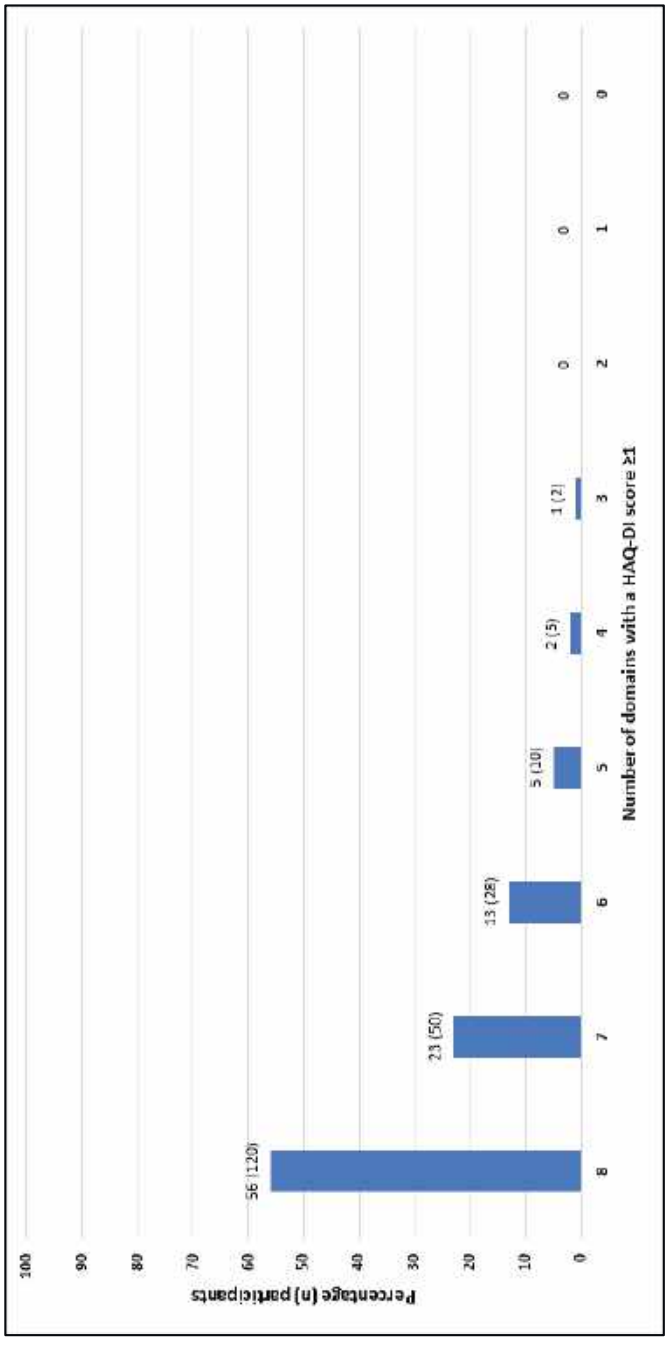


Figure 2 Frequencies of the total number of domains with a HAQ-DI domain score of ≥1 (percentage and number of participants, n=215).

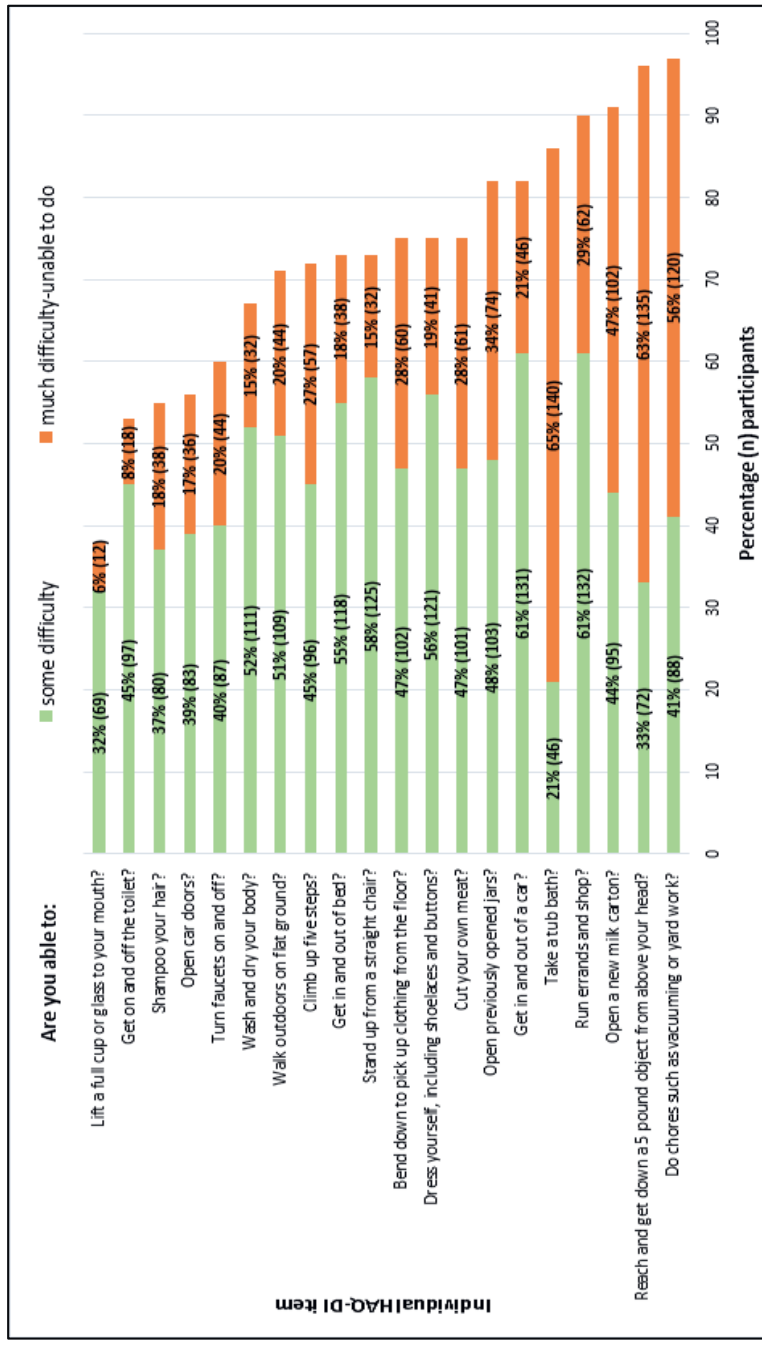


Figure 3 Frequencies of participants experiencing at least some difficulty (score ≥1) per individual item on the HAQ-DI (percentage and number of participants, n=215).

Table 2 Comparison of patient and disease characteristics between HAQ-DI scores <2 and HAQ-DI scores ≥2.

	HAQ-DI <2 (n=157)	**HAQ-DI ≥2 (n=58)**	**p-value**	**mean difference [95% CI][c]**	**OR [95% CI][d]**
Female, n (%)	140 (89)	54 (93)	p=0.39	NA	1.6 [0.5, 5.1]
Age in years, mean (SD)	57.7 (12.7)	61.6 (13.0)	p=0.049	-3.9 [-7.8, -0.02][d]	NA
BMI (kg/m2), mean (SD)	27.4 (5.7)	28.1 (6.8)	p=0.44	-0.8 [-2.8, 1.2] [d]	NA
Single-person household, n (%)	49 (31)	18 (31)	p=0.98	NA	1.0 [0.5, 1.9]
Higher Education, n (%)	50 (32)	12 (21)	p=0.11	NA	0.6 [0.3, 1.2]
Works status: *≤66 years old* (n=154)					
Having a Paid job, n (%)	41 (26.1)	4 (6.9)	p=0.002	NA	0.21 [0.07, 0.6]
Disease duration (years), Mean (SD)	16.6 (11.2) (n=141)	24.9 (15.5) (n=52)	p<0.001	-8.3 [-13.0, -3.7][d]	NA
Difficult-to-treat RA criteria[a], n (%)	34 (42) (n=81)	56 (49) (n=110)	p=0.26	NA	1.45 [0.8, 2.8]
RF positive, n (%)	48 (62) (n=78)	79 (73) (n=109)	p=0.63	NA	1.2 [0.6, 2.4]
ACPA positive, n (%)	51 (64) (n=80)	62 (60) (n=104)	p=0.12	NA	0.6 [0.3, 1.1]
DAS-28[b], mean (SD)	3.1 (1.3) (n=117)	3.1 (1.4) (n=42)	p=0.99	-0.004 [-0.5, 0.5][d]	NA
Number of comorbidities ≥2, n (%)	75 (84) (n=89)	110 (89) (n=124)	p=0.25	NA	1.8 [0.7, 5.0]
Joint replacement surgeries ≥1, n (%)	18 (20)	62 (50)	p=0.018	NA	2.1 [1.1, 3.8]
PROMIS PF-10, mean (SD)	35.9 (3.4)	28.4 (5.0)	p<0.001	7.6 [6.1, 9.0][d]	NA
SF-36 PCS, mean (SD)	31.1 (7.8)	25.1 (6.2)	p<0.001	6.1 [4.0, 8.1][d]	NA
SF-36 MCS, mean (SD)	47.4 (12.2)	44.7 (12.8)	p=0.17	2.6 [-1.1, 6.4][d]	NA
6MWT distance (meters), mean (SD)	332 (82) (n=155)	234 (94)	p<0.001	98 [72, 124][d]	NA

ACPA, anti-citrullinated protein antibodies; BMI, Body Mass Index; DAS-28, Disease Activity Score; Higher education, Bachelor or Master at University (of Applied Sciences); and doctoral degree program at research universities; PROMIS PF-10, Patient Reported Outcomes Measurement Information System Physical Functioning-10; RF, Rheumatoid Factor; SF-36 MCS/PCS, 36-Item Short-Form Health Survey Mental/Physical Component Summary Scale; 6MWT; 6-minute walk test.

[a] Difficult-to-treat RA definition based on Nagy et al. [7].

[b] DAS-28 score is based on the ESR and if the DAS-28 score was based on the CRP score the following calculation was used: DAS28-ESR=3.3928*Ln (DAS-28-CRP)+0.0254 [30].

[c] Independent samples T-test calculating the mean difference and 95% confidence interval.

[d] Odds ratio and 95% confidence interval.

In Table 2, characteristics stratified for individuals with HAQ-DI scores < 2 and those with HAQ-DI scores ≥ 2 are presented including their associations. Advanced age (mean difference −3.9 [95% CI: −7.8, −0.02]), longer disease duration (mean difference −8.3 [95% CI: −13.0, −3.7]), unemployment (OR: 0.21 [95% CI: 0.07, 0.6]), and the presence of one or more joint replacements (OR: 2.1 [95% CI: 1.1, 3.8]) were associated with HAQ-DI scores ≥ 2. Additionally, on average, patients with higher HAQ-DI scores ≥ 2 had a lower PROMIS-PF-10 score (mean difference 7.6 [95% CI: 6.1, 9.0]), a reduced SF-36 PCS (mean difference [95% CI: 6.1 [4.0, 8.1]), and a shorter distance covered in the 6 min walk test (mean difference 98 [95% CI: 72, 124]). No significant differences were observed in any of the other characteristics between the two HAQ-DI score groups.

Discussion

In a subgroup of people with RA, the extent and nature of self-reported functional disability was assessed. The complexity of their condition was illustrated by the considerable proportions of people with multiple comorbidities and fulfilling the criteria for D2T RA [7]. The majority showed to have considerable limitations in almost all the domains of the HAQ-DI. Limitations were most prevalent in the domains of Usual activities, Personal hygiene and Reaching. The extent and nature of the reported disability may indicate the need for support from multiple healthcare professionals meeting the specific needs of this subgroup. Higher HAQ-DI scores seemed to be associated with advanced age, longer disease duration, unemployment, joint replacements, and outcomes for daily functioning and physical QoL, but not with measures of disease activity.

There is a paucity of studies assessing the extent and nature of functional limitations in people with RA, especially for this specific subgroup. Participants in this study showed moderate-to-severe disability, reflected in a mean HAQ-DI of 1.7 (0.5). This finding is partly consistent with an RCT in which people with RA who were hospitalized for multidisciplinary treatment in a rheumatology clinic due to active RA and loss of functional ability showed HAQ-DI values of 1.8 (0.8) and 1.7 (0.6), respectively [37]. However, this study was conducted more than twenty years ago. Furthermore, the HAQ-DI value we observed was significantly higher than the HAQ score of 0.9 (0.5) observed in a recent study, in a subpopulation of D2T RA patients consecutively selected from a hospital population [38]. A lower HAQ-DI score of 1.27 was also observed in a population with generalized osteoarthritis referred for multidisciplinary treatment [39]. This shows that our study population has a high HAQ-DI score, indicating a high clinical burden, although they were treated in primary care and not in a multidisciplinary rehabilitation setting.

In a study by Meesters et al. [15], in which treatment goals of an RA population in rehabilitation care were linked to the ICF, most limitations in functioning were seen within the chapters “Learning and applying knowledge” (d1), “General tasks and demands” (d2), “Communication” (d3), “Mobility” (d4) and “Self-care” (d5). However, not all these chapters can be linked to the domains of the HAQ-DI. Our findings are partly in line with a previous study from our study group in the same population. Here, the treatment goals elicited and prioritized with the PSC were linked to the ICF, in which “Walking”, “Changing body position” and “Grasping” were the most frequently identified ICF codes [16]. However,

the methods for assessing disability using the PSC cannot be compared to a predefined list of activities as defined in the HAQ-DI.

When assessing the severity of the HAQ-DI, one other study also focused on the individual items [40]. This particular study involved an RA population characterized by a relatively favorable health status and absence of serious comorbidities, leading to lower average scores per individual item compared to our specific population [40]. Nevertheless, noteworthy similarities were observed in the items exhibiting the highest disability scores. The three items displaying the highest scores mirrored our study, encompassing challenges related to "Doing chores such as vacuuming or yard work", "Reach and get down a 5-pound object", and "Open a new carton of milk" [40].

The substantial number of participants facing challenges in performing activities of daily living within the domains of Personal hygiene, Reaching, and Usual activities primarily resulted from limitations in a single key item. Within each respective domain, these key items were: "Taking a tub bath", "Doing chores such as vacuuming or yard work", or "Reaching and getting down a 5-pound object from above your head". Although these specific items may require extra attention, it should also be noted that the majority of participants reported at least some difficulty in all other individual items. The only exception here was "Lifting a full cup or glass to your mouth". This broad range of challenges underscores the overall disability experienced by this subgroup, wherein the joints of the upper, lower, or both upper and lower extremities may be affected.

Nearly two-thirds of participants encountered difficulties in a seemingly straightforward lower limb activity, such as "Walking outdoors on flat ground". Conversely, over 90% face challenges in upper extremity activities like opening a milk carton and reaching. These findings strongly indicate that both upper and lower extremity functioning are compromised in the majority of patients.

Furthermore, it is noteworthy that tasks such as getting on and off the toilet may present a complex challenge for this subgroup. This complexity arises from the multifaceted nature of the task, encompassing actions such as transferring, wiping, and washing hands, all of which necessitate adequate functioning of both upper and lower extremities. Even with the use of aids such as a raised toilet or grab rails, achieving independence in performing this

task remains elusive for many. Clinicians and health professionals should be attuned to this complexity, actively acquiring about the specific difficulties individuals encounter in these activities and exploring viable options to enhance independence. Understanding the nuanced challenges within these daily tasks is paramount for tailored interventions and support.

Remarkably, we did not find a difference between the patients with HAQ-DI scores < 2 and those with HAQ-DI scores ≥2 in measures of disease activity as several studies demonstrated this association [9, 25, 26]. This discrepancy might be explained by the relatively high proportion of individuals in our study who could be classified as D2T. It is conceivable that the variation in disease activity among individuals in our study was too small to detect an association between functional disability and disease activity.

This study has a number of limitations. The present findings are restricted to patients with severe functional disability included for an RCT on long-term exercise therapy and thus concerned a selected population that might not be generalizable to the total RA population. People with a relatively positive attitude towards exercise therapy may have been overrepresented. Furthermore, although we endorse the 'Sex and Gender Equity in Research—SAGER—guidelines' no gender analyses were conducted, as our population consisted almost entirely of women. It is known that women are in general more willing to participate in research than men [41] and this could have influenced the results. In well treated people with RA, HAQ-DI scores between men and women are similar [42]. However, with increasing disease duration and severity, people with RA tend to overestimate their functional ability, while RA patients in the early stages of the disease tend to underestimate their functional ability [37, 42]. In an RA population with moderate-to-severe disability, men tended to overestimate their functional ability considerably more than females [43]. Several studies have argued that the interpretation of what people perceive as difficult changes over time and is influenced by consciously and unconsciously made adjustments in the performance of activities in daily living. Since functional disability in general may increase over the disease course, attention to the level and nature of perceived limitations is of paramount importance for clinical practice.

Additionally, due to the predominant representation of females, the advanced age of the participants, and the prevalence of a substantial number of comorbidities within the cohort we faced limitations in conducting meaningful subgroup analyses, which could have offered more nuanced insights into variations in functional disability across specific patient or disease characteristics.

Unfortunately, we did not collect data on the location or number of the affected joints, impeding in-depth analysis about the association of the location or number of affected joints and reported limitations in activities on the HAQ-DI. The shoulder, knee, and elbow joints are known to account for approximately 70% of the total contribution to the HAQ [44], underscoring the involvement of both the upper and lower extremities. Subsequent research should aim to address this gap in information.
Furthermore, it is imperative to underscore that our study relies on cross-sectional data, inherently restricting our ability to infer changes over time. Also, by conducting multiple statistical tests, potential pitfalls are introduced, including an increased risk of Type I errors and the potential for false positive findings. In addition, the absence of a dedicated power analysis underscores the importance of approaching these results with caution.

A strength is that the present study was nationwide and includes a relatively high number of subjects which could also facilitate the generalizability of the results. Furthermore, this is the first study documenting the extent and nature of functional limitations in eight domains of the HAQ for this subgroup. Future research in other subgroups of RA people could provide a more comprehensive insight into the extent to which people with RA experience functional limitations, despite the availability of advanced pharmacological treatment options.

Conclusions

In conclusion, in this RA subgroup with self-reported severe disability, there are profound functional limitations in all domains, with limitations in the domains of Personal hygiene and Reaching being the most prevalent. Therefore, a comprehensive assessment of all areas of daily activities in this RA subgroup is necessary for daily clinical practice. Insight into the domains of functional disability could lead physicians and health professionals to target relevant and modifiable factors to regain and maintain function and prevent disability. In addition, the extent and nature of the reported disability may indicate the need for nonpharmacological care that meets the specific needs of this subgroup. Higher HAQ-DI scores seemed to be associated with advanced age, longer disease duration, unemployment, joint replacements, and outcomes for daily functioning and physical QoL, but not with measures of disease activity. However, additional research is imperative to validate and substantiate these identified associations.

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Author Contributions

Conceptualization, M.G.J.G., C.H.M.v.d.E. and S.F.E.v.W.; Methodology,M.G.J.G., S.F.E.v.W., M.A.T.v.W. and M.M.H.T.; Software, Not applicable for this study; Validation, M.G.J.G., D.v.S., W.F.P. and C.H.M.v.d.E., Formal Analysis, M.M.H.T. and M.A.T.v.W.; Investigation, M.G.J.G., S.F.E.v.W., M.M.H.T., M.A.T.v.W. and C.H.M.v.d.E.; Resources, M.M.H.T., M.A.T.v.W. and D.v.S.; Data Curation, M.M.H.T. and M.A.T.v.W.; Writing—Original Draft Preparation, S.F.E.v.W. and M.M.H.T.; Writing—Review and Editing, all authors.; Visualization, all authors; Supervision, M.G.J.G., S.F.E.v.W.,W.F.P. and C.H.M.v.d.E.; Project Administration, S.F.E.v.W. and M.G.J.G.; Funding Acquisition, S.F.E.v.W., M.G.J.G. and C.H.M.v.d.E. All authors have agreed to be personally accountable for their own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, are appropriately investigated, resolved, and documented. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Medical Ethical Committee Leiden-Den Haag-Delft (METC LDD;) of the Leiden University Medical Center (protocol code L-EXTRA: NL69866.058.19 and approved on 11 July 2019). All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Leiden University Medical Center (protocol code L-EXTRA: NL69866.058.19).

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7

Chapter 7

The use of PROMIS measures in clinical studies in patients with inflammatory arthritis: a systematic review

Max M.H. Teuwen[1], Isabelle R.E. Knaapen[1], Thea P.M. Vliet Vlieland[1], Jan W. Schoones[2], Cornelia H.M. van den Ende[3,4], Salima F.E. van Weely[1], Maaike G.J. Gademan[1,5]

1. Department of Orthopaedics, Rehabilitation and Physical Therapy, Leiden University Medical Center, Leiden, The Netherlands;
2. Directorate of Research Policy, Leiden University Medical Center, Leiden, The Netherlands;
3. Department of Research, Sint Maartenskliniek, Nijmegen, The Netherlands;
4. Department of Rheumatology, Radboud University Medical Center, Nijmegen, The Netherlands;
5. Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.

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Abstract

Objectives: Although the use of Patient-Reported Outcomes Measurement Information System (PROMIS) measures is widely advocated, little is known on their use in patients with inflammatory arthritis. We systematically describe the use and outcomes of PROMIS measures in clinical studies involving people with rheumatoid arthritis (RA) or axial spondyloarthritis (axSpA).

Methods: A systematic review was conducted according to the PRISMA guidelines. Through a systematic search of nine electronic databases, clinical studies including patients with RA or axSpA and reporting the use of PROMIS measure were selected. Study characteristics, details of PROMIS measures and their outcomes, if available, were extracted.

Results: In total, 29 studies described in 40 articles met the inclusion criteria, of which 25 studies included RA patients, three studies included axSpA patients and one study included both RA and axSpA patients. The use of two general PROMIS measures (PROMIS Global Health, PROMIS-29) and 13 different domain-specific PROMIS measures was reported, of which the PROMIS Pain Interference (n = 17), Physical Function (n = 14), Fatigue (n = 13), and Depression (n = 12) measures were most frequently used. Twenty-one studies reported their results in terms of T-scores. Most T-scores were worse than the general population mean, indicating impairments of health status. Eight studies did not report actual data but rather measurement properties of the PROMIS measures.

Conclusion: There was considerable variety regarding the different PROMIS measures used, with the PROMIS Pain interference, Physical function, Fatigue, and Depression measures being the most frequently used. In order to facilitate the comparisons across studies, more standardization of the selection of PROMIS measures is needed.

Keywords: Systematic review; PROMIS; Patient-reported outcome measures; Rheumatoid arthritis; Axial spondyloarthritis.

Plain English summary

Apart from clinical, laboratory tests, or imaging, patient-reported outcome measures (PROMs) are essential to evaluate the outcomes of inflammatory arthritis and its management. With the Patient-Reported Outcomes Measurement Information System (PROMIS), PROMs can be measured in a uniform and standardized way. PROMIS covers specific and generic health domains and are relevant for various patient populations. Specific PROMIS measures such as Physical Function, Fatigue, Sleep Disturbance, or Depression can be used to measure a more specific health domain than the general measures such as PROMIS Global Health. Although the use of PROMIS measures is widely advocated, little is known on their actual use in patients with inflammatory arthritis. In this systematic literature review, we wanted to describe the use and outcomes of PROMIS measures in clinical studies involving people with rheumatoid arthritis or axial spondyloarthritis. This systematic literature review found that PROMIS measures are currently not often used in clinical studies in these patient groups and that there is a large variety regarding the use of specific PROMIS measures. To facilitate the comparisons of outcomes across studies, more standardization of the use of specific PROMIS measures is needed.

Introduction

Rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA) are two forms of inflammatory arthritis that can lead to pain, stiffness, fatigue, limitations in functioning, and participation in a considerable proportion of patients, despite the availability of effective drug treatments [1–3]. It is beyond doubt that this has a major impact on the quality of life of these patients [1–3].

Apart from clinical, laboratory, or imaging parameters, patient-reported outcome measures (PROMs) are essential to evaluate the outcomes of inflammatory arthritis and its management. To date, numerous PROMs, either generic or disease-specific, are used in clinical care and research regarding inflammatory arthritis. However, some of the widely used legacy measures that are based on the classical test theory are criticized for a lack of standardization, precision, and/or comparability of scores across studies and diseases [4, 5]. To overcome these limitations, in 2007, the Patient-Reported Outcomes Measurement Information System (PROMIS) became available [6]. PROMIS measures are item-response theory-based questionnaires (Item Banks, Short Forms or Computer Adaptive Tests) that cover specific and generic health domains and are relevant for various patient populations. All PROMIS measures use a standardized metric, called a T-score, centered around the general population, which enhances the interpretability of these scores.

PROMIS measures have been applied in general populations and in people with different physical conditions such as critical illness, spinal surgery, low back pain, cancer, and chronic pain [7–12]. For inflammatory arthritis patients, the use of PROMIS measures seems to be appropriate as well, where several PROMIS measures are used since its introduction in 2007. Recently, the International Consortium for Health Outcomes Measurement (ICHOM) promoted the use of PROMIS Pain Interference, General Health, Physical Function, and Fatigue measures as part of routine outcome measurement for patients with inflammatory arthritis [13]. This more standardized way of reporting PROMIS outcomes facilitates new options to compare the performance of health care for inflammatory arthritis on a global scale, allowing health care professionals to learn from each other and to further improve the health care for inflammatory arthritis patients.

Little is known so far about the extent and nature of their actual use in clinical research in patients with inflammatory arthritis. Thus, the aim of this review was to systematically

determine the use and outcomes of PROMIS measures in clinical studies including patients with RA and/or axSpA. The outcomes of PROMIS measures were included to assess whether the PROMIS measures depict the relatively worse health status of RA and axSpA patients.

Methods

Study design

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14], with the exception of the PRISMA item on risk of bias assessments, as the methodological quality of the studies was deemed less relevant given the exploratory nature of the literature review.

Search strategy

A trained librarian (JS) performed a literature search in nine electronic databases (PubMed, MEDLINE, Embase, Web of Science, Cochrane Library, Emcare, PsycINFO, Academic Search Premier, Google Scholar) on July 29, 2022. The search strategy consisted of the combination of the disease concepts (RA, AxSpA and inflammatory arthritis) with PROMIS. Not only controlled subject terms such as MeSH terms were applied, but also various free text words describing the search concepts were used. The search was limited to articles published from 2007 onwards, as PROMIS became available in that year. The search strategy is presented in Supplement 1. The identified records were imported into a software application (Rayyan (http://rayyan.qcri.org) [15] and duplicates were removed. In addition, studies were identified through an indirect approach by screening the references of included studies and those of relevant systematic reviews resulting from the search.

Selection criteria

Inclusion criteria: Original clinical studies (a) reporting the use of one or more PROMIS measures; (b) including patients with RA and/or axSpA aged 18 years or above; (c) written in English, French, German or Dutch.

Exclusion criteria: Studies including patients with multiple diagnoses, but not reporting the information on RA or axSpA patients separately. No limitations were formulated on the type of study design (e.g., retrospective studies, prospective studies, randomized controlled trials).

Selection process

Records retrieved from the search were screened in two phases. In the first phase, all identified records were screened by checking the title and abstract by two researchers (MT, IK) according to the abovementioned eligibility criteria using the online Rayyan® software [15]. Records were scored as most likely eligible, possibly eligible and not eligible. Records that were scored as not eligible were excluded. Disagreements were resolved by discussion between the two researchers and if no agreement was found the record was deemed as eligible for the second phase of screening. Subsequently, 10% of all records in the first phase (title and abstracts) were screened by a third researcher (TVV) to ensure the quality of the selection process.

In the second phase, full-text articles were retrieved and independently screened by the same two researchers, using the same eligibility criteria. For that purpose, the outcomes of the screening were entered into a pre-defined database with the inclusion and exclusion criteria. Disagreements were resolved by discussion between the two researchers and if no agreement was found, a third researcher was consulted (TVV or MG). Fifty percent of the screening of the full-text papers was checked by a third researcher (MG). The third reviewer was a supervisor (TVV /MG), who was engaged to further ensure the quality of the screening process. For feasibility reasons, given the total amount of titles and abstracts versus full-text papers, 10% and 50% of the selection and extraction processes was checked.

Data extraction

A pre-defined data extraction form was used to systematically extract information from the full-text articles that were ultimately selected. One researcher extracted the data (MT or IK), a second researcher checked this extraction (MT or IK). Again, a third researcher checked the data extraction of 50% of the papers to ensure the data were correctly extracted (MG).

Regarding the study characteristics, information on the first author, year of publication, country, study design (cross-sectional study, longitudinal cohort study, controlled or uncontrolled clinical trial, other; based on definition of the original study) and population (registry, community or clinic) was retrieved. With respect to the study populations we collected: type of inflammatory arthritis (RA, axSpA or both), the number of patients, general patient characteristics (mean age, sex, disease duration).

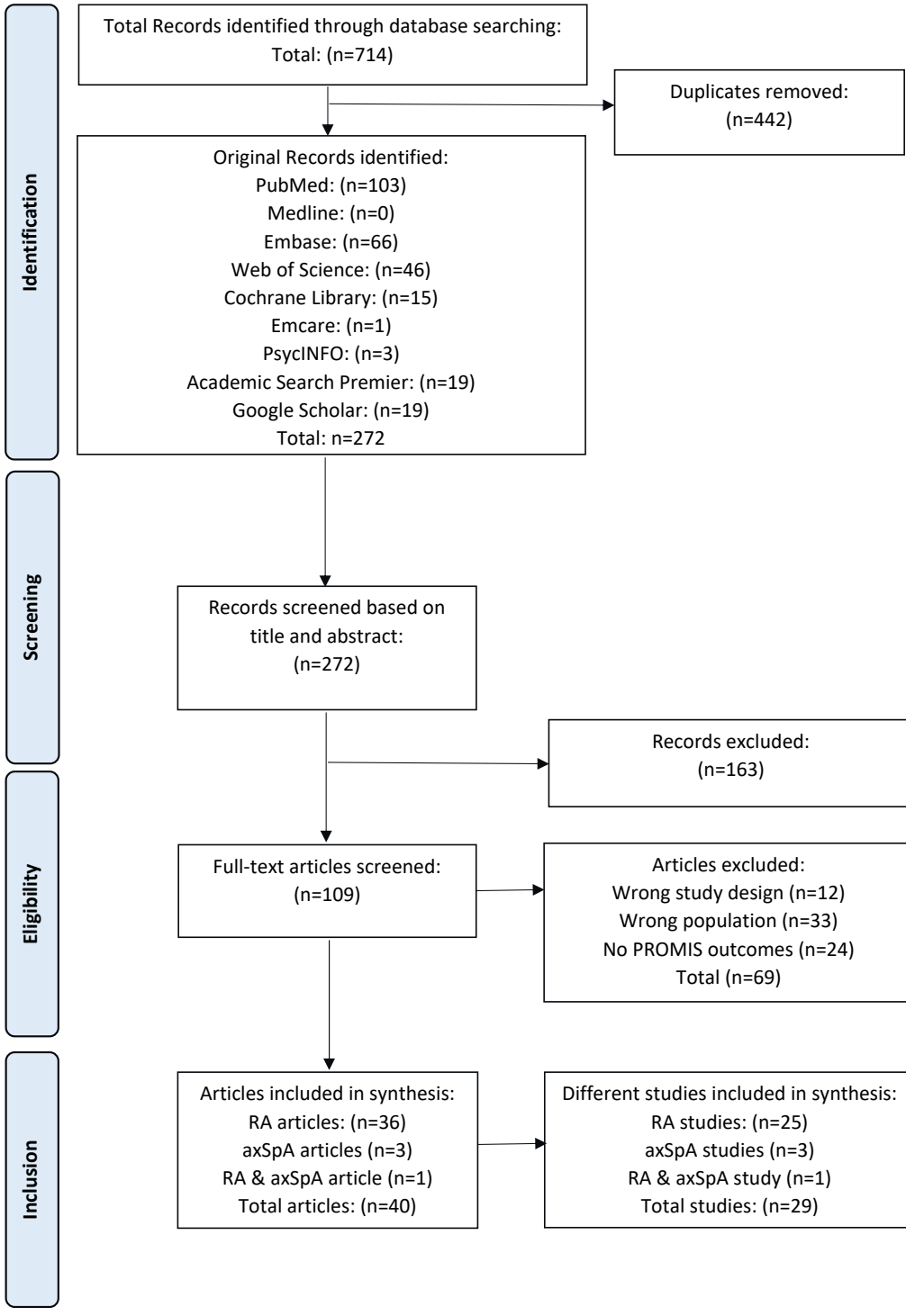
We defined articles as individual papers unless the data of two or more articles were gathered in the same community, clinic(s) or registry, and the sample sizes and general patient characteristics (age, sex distribution) were exactly the same, in that case we addressed these articles as one single study. The date of the first publication was used for the chronological ordering of the studies. However, if one of these publications included T-scores and the other publications did not, the date of the publication reporting on T-scores was used.

The name of the PROMIS measures (Item Banks, Short Forms, Computer Adaptive Tests) used with version number was recorded and checked with the website of healthmeasures.net, accessed on August 1, 2022. If the name of the reported PROMIS measure was not registered, the measure was not taken into account. Also the results of T-score metrics were extracted, if available. For T-scores a normalized distribution (T-score 0–100, standardized mean 50, standard deviation 10) is used. A value of 50 is considered as the mean score of the general population with a standard deviation of 10. For some PROMIS measures a score higher than 50 indicates a better outcome (e.g., PROMIS Ability to Participate in Social roles and Activities, Physical Function, Satisfaction with Social roles and Activities), whereas for others a score higher than 50 means a worse outcome (e.g., Anger, Anxiety, Fatigue, Pain Behavior, Pain Intensity, Pain Interference, Sleep Disturbance, Sleep-Related Impairment, Depression). If a PROMIS measure was administered multiple times in one study and likewise reported, the results at baseline were extracted. If the results of a specific PROMIS measure were reported in multiple articles that were grouped in one study, and there was a difference between T-scores smaller than 0.5, the score reported in the first publication was extracted. In case of any scores that were unclear, the first author of the article was contacted, to confirm the calculation.

Results

The search identified initially 714 records, which after deduplication resulted in a set of 272 records. The first screening resulted in the exclusion of 163 records (Fig. 1). After the screening of the remaining 109 full-text articles, 69 were excluded. Thus, in total, 40 articles were included [16–55], reporting on 29 studies, including 25 studies in RA patients three studies in axSpA patients and one study on both RA and axSpA patients. The flow of the screening process is shown in Fig. 1.

Figure 1 Flowchart of screening process.



The publication years of the studies ranged from 2011 up to 2022, with relatively more studies being published in recent years. Of the 29 studies, three studies were published in 2011–2015, 13 studies in 2015–2019 and 13 studies in 2020-present.

The characteristics of the 29 included studies (total number of 22,855 patients) are summarized in Table 1. Overall, most of the studies originated from the US (23 of 29 studies; 79.3%). The study designs included cross-sectional studies (10 of 29 studies, 34.5%), longitudinal cohort studies (15 of 29 studies; 51.7%), randomized controlled trials (two of 29 studies, 6.9%), or other (one pilot study 3.4% and one cross-over study, 3.4%).

Table 1 shows the various PROMIS measures identified in the included studies. In total, 17 different PROMIS measures were identified in this review, consisting of two general health measures (PROMIS Global Health and PROMIS-29) and 13 measures pertaining to a specific health domain. The latter included the PROMIS Physical Function, Fatigue, Pain Interference, Pain Intensity, Pain Behavior, Sleep Disturbance, Sleep-Related Impairment, Satisfaction with Social Roles and Activities, Ability to Participate in Social roles and Activities, Anxiety, Anger, Depression, and Self-Efficacy Managing Symptoms. The four most frequently used measures were: PROMIS Pain Interference (17 studies), Physical Function (14 studies), Fatigue (13 studies), and Depression (12 studies).

Table 2 shows the details of the specific versions of PROMIS measures being used, classified according to their typology into Item Banks, Computer Adaptive Tests (CATs), and Short Forms. Some of the variation regarding the versions can be explained by the publication dates, with more recent articles reporting more recent versions of a similar PROMIS instrument. Other sources of variation include the precise naming and the number of items used.

Table 1 Characteristics and used PROMIS measures of clinical studies in patients with axSpA and RA.

Study	Country	1 CS 2 LC 3 RCT 4 Other	1 RA 2 axSpA	N	Female (%)	Population	Age Mean (SD)	Years since diagnosis Mean (SD)
Gavigan et al. 2022 [55]	USA	2	2	195	87.0	Registry: Arthritis Power Registry	47.6 (10.6)	38.6(11.2)[a]
Becker et al. 2021 [16]	USA	1	1	20 12	65.0 65.0	Community: used Pain interference Community: used Sleep Disturbance	53.2 (11.4) 55.0 (8.5)	9.2 (7.4) 13.3 (12.0)
Bingham et al. 2021 [17]	USA	2	1	11	91.0	Clinic: Johns Hopkins Arthritis Centre	55.0 (12.0)	20.0 (10.0)
Cano-García et al. 2021[e] [18]	SP	1	1 2	50 51	90.0 51.0	Clinic: RA patients Clinic: axSpA patients	55.1 (13.6) 52.5 (12.1)	14.3 (7.1) 13.0 (6.1)
Lee et al. 2021 [19]	USA	2	1	3949	83.0	Registry: The National Databank for Rheumatic Diseases (FORWARD) registry	65.4 (11.9)	21.7 (12.6)
Craig et al. 2020[f] [20-22]	USA	2	1	196 262	81.0 82.0	Clinic: Johns Hopkins Arthritis Centre Clinics: Johns Hopkins, The Hospital for Special Surgery, University of Alabama	54.8 (13.4) 56.6 (13.9)	11.0 (10.0) 13.2 (11.4)
Gavigan et al. 2020 [23]	USA	1	1	249	92.0	Registry: Arthritis Power Registry	51.7 (11.0)	11.0 (9.5)
Heisler et al. 2020 [24]	USA	2	1	263	81.8	Clinics: five US academic medical centers	54.7 (13.8)	9.8 (11.9)
Hitchon et al. 2020 [25]	USA	1	1	150	84.7	Clinic & Community: Arthritis Center in Winnipeg	59.8 (11.7)	41.7 (14.9)[a]
Hwang et al. 2020 [26]	USA	2	2	119	69.0M	Clinic: University of Texas Health Science Center	50.9 (14.77)	25.5 (13.3)
Katz et al. 2020 [27]	USA	2	1	3848	83.1	Registry: The National Databank for Rheumatic Diseases (FORWARD) registry	64.9 (12.0)	20.8 (12.7)
Liew et al. 2020 [28]	USA	2	2	203	66.0M	Clinic: University of California, San Francisco	46.4 (12.5)	22.9 (12.4)
Prodinger et al. 2020 [29]	Ger UK	1	1	180 535	91.4 74.2	Clinic: sample from Germany Clinic: Sample From UK	49.0 (13.8) 68.3 (10.0)	13.5 (12.2) 19.8 (13.0)
Bingham et al. 2019 [30, 31]	USA	1	1	348	348	Clinics: Johns Hopkins, The Hospital for Special Surgery, University of Alabama	57.0 (14.0)	14.0 (11.0)

Table 1 (continued) Characteristics and used PROMIS measures of clinical studies in patients with axSpA and RA.

Study	Country	1 CS 2 LC 3 RCT 4 Other	1 RA 2 axSpA	N	Female (%)	Population	Age Mean (SD)	Years since diagnosis Mean (SD)
Crins et al. 2019 [32, 33]	NL	1	1	2029	69.0	Clinic: Outpatient patients from Reade and Leuven, used Pain Interference	59.0 (13.0)	1-12 months 2% 1-2 years 7% 2-5 years 16% >5 years 75%[c]
				1554	69.0	Clinic: Outpatient patients from Reade and Leuven, used Pain behavior	59.0 (12.0)	1-12 months 2% 1-2 years 6% 2-5 years 15%
Izadi et al. 2019 [34]	USA	2	1	595	83.0	Clinic: University of California, San Francisco	56.8 (15.3)	
Mahmoud et al. 2019 [35]	EG	1	1	120	94.0	Clinic: Outpatient clinic Cairo University	41.5 (11.1)	6.3 (7.3)
Wohlfahrt et al. 2019 [36]	USA	2	1	156	82.1	Clinics: five US academic medical centers	54.6 (13.6)	10.0 (12.6)
Alleva et al. 2018 [37]	UK/NL	3	1	84	100.0	Community: Female RA population	44.8 (12.5)	11.3 (10.9)
Bartlett et al. 2018[g] [38, 30]	USA	1	1	200	84.0	Community: Creakyjoints.org	51.0 (12.0)	10.0 (10.0)
				52	87.0	Clinic: Johns Hopkins Arthritis Centre patients	53.0 (14.0)	15.0 (11.0)
				32	72.0	Clinics: Johns Hopkins, Hospital for Special Surgery,	54.0 (13.0)	13.0 (10.0)
Katz et al. 2018 [39]	USA	3	1	96	84.0	Clinic: University of California, San Francisco	54.8 (13.4)	14.8 (12.3)
Mollard et al. 2018 [40]	USA	4	1	63		Clinic: Rheumatology and Arthritis Investigational Network Database	>18 years[d]	
Bacalao et al. 2017 [41]	USA	2	1	119	91.0	Clinic: Northwestern University Feinberg School of Medicine	57.0(21.0-77.0)[b]	11.0(0-52)[b]
Katz et al. 2017 [42]	USA	2	1	4346	83.0	Registry: The National Databank for Rheumatic Diseases (FORWARD) registry	64.0 (12.0)	20.0 (13.0)
Wahl et al. 2017 [43]	USA	2	1	326	81.6	Clinic: University of California, San Francisco	59.0 (14.0)	12.0(5.0-22.0)[b]

Table 1 (continued) Characteristics and used PROMIS measures of clinical studies in patients with axSpA and RA.

Study	Country	1 CS 2 LC 3 RCT 4 Other	1 RA 2 axSpA	N	Female (%)	Population	Age Mean (SD)	Years since diagnosis Mean (SD)
Askew et al. 2016 [44-47]	USA	2	1	521	81.0	Registry: The Arthtritis Rheumatism and Aging Medical Information System (ARAMIS) registry	88% ≥50[c]	
Bjorner et al. 2014 [48]	USA	4	1	223	35.0M	Community: contacted RA patients	56.0 (10.0)	
Oude Voshaar et al. 2014 [49-51]	NL	2	1	690	63.6	Registry: The Dutch Rheumatoid Arthritis Monitoring (DREAM)	56.8 (11.8)	
				557	52.6	Community: contacted US RA sample	56.7 (10.9)	
Fries et al. 2011 [52-54]	USA	2	1	451	81	Registry: The Arthtritis Rheumatism and Aging Medical Information System (ARAMIS) registry	65	

Table 1 (continued) Characteristics and used PROMIS measures of clinical studies in patients with axSpA and RA.

Study	General		Promis measures of a specific domain										
	GH	P-29	Physical Function	Fatigue	Pain IF	Pain BH	Pain IT	Sleep Disturbance/ Sleep-Related	Satisfaction with Social Roles and	APS	Anxiety /Anger	Depression	SEMS
Gavigan et al. 2022 [55]			x		x			x					
Becker et al. 2021 [16]					x			x					
Bingham et al. 2021 [17]				x	x								
Cano-García et al. 2021[e] [18]										x			
Lee et al. 2021 [19]					x								
Craig et al. 2020[f] [20-22]			x	x	x			x		x	x	x	
Gavigan et al. 2020 [23]			x	x	x			x	x				
Heisler et al. 2020 [24]	x				x			x			x	x	
Hitchon et al. 2020 [25]											x	x	
Hwang et al. 2020 [26]	x		x	x	x		x					x	
Katz et al. 2020 [27]					x								
Liew et al. 2020 [28]											x		
Prodinger et al. 2020 [29]			x										
Bingham et al. 2019 [30, 31]		x	x	x	x					x		x	
Crins et al. 2019 [32, 33]					x	x							
Izadi et al. 2019 [34]			x										
Mahmoud et al. 2019 [35]			x	x	x	x	x				x	x	
Wohlfahrt et al. 2019 [36]	x			x	x	x	x				x	x	

Table 1 (continued) Characteristics and used PROMIS measures of clinical studies in patients with axSpA and RA.

Study	General		Promis measures of a specific domain										
	GH	P-29	Physical Function	Fatigue	Pain IF	Pain BH	Pain IT	Sleep Disturbance/ Sleep-Related	Satisfaction with Social Roles and	APS	Anxiety /Anger	Depression	SEMS
Alleva et al. 2018 [37]											x	x	
Bartlett et al. 2018[g] [38, 30]		x	x	x	x					x		x	
Katz et al. 2018 [39]				x	x								
Mollard et al. 2018 [40]													x
Bacalao et al. 2017 [41]			x	x	x							x	
Katz et al. 2017 [42]		x											
Wahl et al. 2017 [43]			x										
Askew et al. 2016 [44-47]			x	x	x								
Bjorner et al. 2014 [48]			x	x								x	
Oude Voshaar et al. 2014 [49-51]			x										
Fries et al. 2011 [52-54]			x	x									
N articles axSpA patients	1	0	2	1	2	0	1	1	0	1	1	1	0
N studies axSpA patients	1	0	2	1	2	0	1	1	0	1	1	1	0
N articles RA patients	2	3	20	15	18	3	2	8	1	6	8	13	1
N studies RA patients	2	3	12	12	15	2	2	6	1	4	6	11	1

APS, Ability to Participate in Social Roles and Activities; axSpA, axial spondyloarthritis; CS, cross-sectional study; EG, Egypt; GH, Global Health; LC, longitudinal cohort study; M, male participants; NL, Netherlands; N, number; Pain BH, Pain Behavior; Pain IT, Pain Intensity; Pain IF, Pain Interference; P-29, PROMIS-29; RA, rheumatoid arthritis; RCT, randomized controlled trial; SEMS, Self-efficacy Managing Symptoms; SP, Spain; SD, standard deviation; UK, United Kingdom; USA, United States of America. [a] Age at diagnosis. [b] Median (range). [c] Mean and median not available: a percentage of the total sample with a value. [d] Mean and median and percentage not available: value based on inclusion criteria; [e] This study reported on one axSpA population and one RA population. In both populations the same PROMIS measure: Ability to Participate in Social roles and Activities (APS) was used and was therefore counted as one study in the RA patients group and as one study in the axSpA patients group. [f] Craig et al. 2020 describes 2 populations, one population, describing 196 patients, was included in Bartlett et al. 2020a and Direnzo et al. 2020, the other population describing 262 patients was only included in Craig et al. 2020. [g] Bingham et al. 2019 describes 2 populations, one population, describing 348 patients, was included in Bartlett et al. 2020b and one population of 200 was included in Bartlett et al. 2018. The populations of 52 and 32 patients were only included in Bartlett et al. 2018.

Table 2 PROMIS measure versions used in axSpA and RA populations.

PROMIS measure used	N of articles	N of studies	Publication year	Reference of articles
PROMIS Global Health (GH)	**3**	**3**		
PROMIS Global Health Short Form[c]	1	1	2021	[24]
PROMIS Global Health Short Form version 1.1[a]	1	1	2021	[26]
PROMIS Global Health version 1.1[a]	1	1	2019	[36]
PROMIS-29	**3**	**3**		
PROMIS Adult profile-29a[c]	2	2	2019, 2017	[30, 42]
PROMIS Adult profile-29 (v2.0)[a]	1	1	2020	[31]
PROMIS Physical Function	**22**	**14**		
PROMIS Physical Function[c]	1	1	2021	[46]
PROMIS physical Function Item Bank[c]	1	1	2014	[49]
PROMIS CAT Physical Function[c]	5	4	2022, 2020, 2020, 2020, 2017	[55, 20, 22, 23, 41]
PROMIS CAT Physical Function 10-item	1	1	2014	[50]
PROMIS CAT Physical Function (v.1.0)	1	1	2020	[21]
PROMIS Physical Function 4-items Short Form	1	1	2020	[29]
PROMIS Physical Function 6-items Short Form	1	1	2020	[29]
PROMIS Physical Function 8-items Short Form	2	2	2014, 2011	[48, 52]
PROMIS Physical Function 10-items Short form	3	3	2020, 2015, 2011	[29, 51, 53]
PROMIS Physical Function 10a Short Form	3	3	2019, 2019, 2017	[34, 35, 43]
PROMIS Physical Function 12a Short Form (v1.0)[b]	1	1	2020	[26]
PROMIS Physical Function 20-items Short Form	4	3	2020, 2016, 2011, 2015	[29, 47, 53, 54]
PROMIS Physical Function 20a Short Form	1	1	2019	[30]
PROMIS Physical Function 20a Short Form (v 1.0)[a]	2	2	2020, 2020	[21, 31]
PROMIS Fatigue	**16**	**13**		
PROMIS Item Bank Fatigue[c]	1	1	2021	[17]
PROMIS CAT Fatigue[c]	5	4	2020, 2020, 2020, 2019, 2017	[20, 22, 23, 36, 41]
PROMIS CAT Fatigue (v.1.0)	1	1	2020	[21]
PROMIS Fatigue Short Form (version 1)	2	2	2020, 2016	[26, 45]
PROMIS Fatigue 4a Short Form	1	1	2019	[35]
PROMIS Fatigue 7a Short Form	2	2	2019, 2018	[30, 39]
PROMIS Fatigue 7a Short Form (v 1.0)	4	4	2020, 2020, 2018, 2021	[21, 31, 38, 46]
PROMIS Fatigue 8-items Short Form	1	1	2014	[48]
PROMIS Fatigue 8a Short Form	1	1	2019	[30]
PROMIS Fatigue 8a Short Form (v 1.0)	2	2	2020, 2018	[31, 38]
PROMIS Pain Interference (Pain IF)	**20**	**17**		
PROMIS Pain Interference Item Bankc	4	4	2021, 2021, 2021, 2016	[16, 17, 19, 44]
PROMIS Pain Interference Item Bank (v 1.1)[a]	2	1	2019, 2020	[32, 33]
PROMIS CAT Pain Interference[c]	7	6	2022, 2020, 2020, 2020, 2020, 2019, 2017	[55, 20, 22-24, 36, 41]
PROMIS CAT Pain Interference (v1.0)	1	1	2020	[21]
PROMIS Pain Interference 4a Short Form	1	1	2019	[35]
PROMIS Pain Interference 4 items Short Form	1	1	2020	[27]
PROMIS Pain Interference 8-items Short form	1	1	2018	[39]
PROMIS Pain Interference 8a Short Form	1	1	2019	[30]
PROMIS Pain Interference 8a Short Form (v 1.0)[a]	3	3	2020, 2020, 2020	[21, 26, 31]
PROMIS Pain Interference 6b-item Short Form (version 1.1)[a]	1	1	2021	[46]
PROMIS Pain Behavior (Pain BH)	**3**	**2**		[32, 33, 36]
PROMIS Pain Behavior Item Bank (v.1.1)[a]	2	1	2019, 2020	[32, 33]
PROMIS CAT Pain Behavior[c]	1	1	2019	[36]

Table 2 (continued) PROMIS measure versions used in axSpA and RA populations.

PROMIS measure used	N of articles	N of studies	Publication year	Reference of articles
PROMIS Pain Intensity (Pain IT)	**3**	**3**		
PROMIS Pain Intensity Short Form (v1.0)	1	1	2020	[26]
PROMIS Pain Intensity 3a Short Form	2	2	2019, 2019	[35, 36]
PROMIS Sleep Disturbance/Sleep-Related Impairment	**9**	**7**		
PROMIS Sleep Disturbance Item Bank (v1.0)	1	1	2021	[16]
PROMIS CAT Sleep Disturbance[c]	5	4	2020, 2020, 2020, 2020, 2019	[20, 22-24, 36]
PROMIS CAT Sleep Disturbance (v.1.0)	1	1	2020	[21]
PROMIS CAT Sleep-Related Impairment[c]	1	1	2019	[36]
PROMIS CAT Sleep Interference[b]	2	2	2022, 2020	[55, 20]
PROMIS Sleep Disturbance 4a Short Form	1	1	2019	[35]
PROMIS Sleep Disturbance 4a Short Form (v.1.0)	1	1	2020	[21]
PROMIS Satisfaction with Social roles and Activities	**1**	**1**		
PROMIS CAT Satisfaction with Social Roles[c]	1	1	2020	[20]
PROMIS Ability to Participate in Social roles and Activities (APS)	**6**	**4**		
PROMIS CAT Participation in Social Roles and Activities[b]	1	1	2020	[20]
PROMIS CAT Ability to Participate in Social Participation[b]	1	1	2020	[22]
PROMIS CAT Ability to Participate in Social Roles (v2.0)[b]	1	1	2020	[21]
PROMIS Ability to Participate in Social Roles and Activities 8a Short Form (v.2.0)	3	3	2021, 2020, 2020	[18, 21, 31]
PROMIS Participation in Social Roles and Activities 8a Short Form	1	1	2019	[30]
PROMIS Anxiety / Anger	**9**	**7**		
PROMIS Anxiety Short Form[b]	1	1	2018	[37]
PROMIS Anxiety Short Form 4a	1	1	2019	[35]
PROMIS Anxiety 4a Short Form (v.1.0)[a]	1	1	2020	[21]
PROMIS Anxiety Short Form (6-items)	1	1	2020	[28]
PROMIS Anxiety 8a Short Form	1	1	2020	[25]
PROMIS CAT Anxiety[c]	4	3	2020, 2020, 2020, 2019	[20, 22, 24, 36]
PROMIS CAT Anxiety (v1.0)[c]	1	1	2020	[21]
PROMIS CAT Anger[c]	1	1	2020	[20]
PROMIS Depression	**14**	**12**		
PROMIS Item Bank Depression[c]	1	1	2014	[48]
PROMIS Emotional Distress-Depression Item Bank[c]	1	1	2011	[52]
PROMIS CAT Depression[c]	5	4	2020, 2020, 2020, 2019, 2017	[20, 22, 24, 36, 41]
PROMIS CAT Depression (v1.0)[c]	1	1	2020	[21]
PROMIS Depression Short Form[c]	1	1	2018	[37]
PROMIS Depression 4a Short Form	1	1	2019	[35]
PROMIS Depression 8a Short Form	2	2	2020, 2019	[25, 30]
PROMIS Depression 8a Short Form (v.1.0)	1	1	2020	[21]
PROMIS Emotional Distress-Depression Short Form (v1.0)	1	1	2020	[26]
PROMIS Self-Efficacy Managing Symptoms (SEMS)	**1**	**1**		
PROMIS Self-Efficacy Managing Symptoms (P-SEMS)[c]	1	1	2018	[40]

axSpA, axial spondyloarthritis; CAT, Computer Adaptive Test; N, number; RA, rheumatoid arthritis.
[a] Version other than reported on website https://www.healthmeasures.net/ [accessed 1 August 2022].
[b] Name of the instrument is different from the one reported on the website https://www.healthmeasures.net/ [accessed 1 August 2022).
[c] Description is unclear, instrument cannot be linked to a specific PROMIS instrument.

In Table 3 the T-scores of the PROMIS measures are presented, classified according to the health domain which they represent. In total, eight of the 29 studies did not report actual outcomes of PROMIS measures in terms of T-scores, but reported on their psychometric properties (e.g., the validity, reliability, correlations with other questionnaires, responsiveness, meaningful change) only. The 26 articles presenting actual PROMIS data described the results from 21 studies.

We contacted the authors of one study [18] as the reported score differed considerably from other reported scores (T-score PROMIS Ability to Participate in Social Roles) with the authors confirming its accuracy. For PROMIS measures where a higher score denotes better health, the mean T-scores were >50 in only one of the 24 reported scores, reflecting the overall poorer health status of people with RA and axSpA. For PROMIS measures where a lower score indicates better health, the mean T-scores were <50 in six of the 67 reported scores.

There were four PROMIS measures of which actual T-scores were reported in 10 or more articles: PROMIS Physical function: range mean 30.6–46.6, PROMIS Fatigue: range 51.1–66.0, PROMIS Depression: range 45.3–57.7, and PROMIS Pain Interference: range 52.2–65.8, overall indicating poor health.

Table 3 T-scores (SD) of PROMIS measures in populations with axSpA and RA.

Study and articles within the study reporting T-scores	Articles or cohorts within the study Reporting PROMIS outcome	GH	P-29	Physical Function	Fatigue	Pain IF	Pain BH	Pain IT	Sleep Disturbance/ Sleep-Related Impairment[i]	Satisfaction with Social Roles and Actitvities	APS	Anxiety	Depression
Gavigan et al. 2022 [55]				36.6 (6.4)		65.8 (6.2)			60.6 (8.2)				
Cano-García et al. 2021 [18]	RA population[18] axSpA population [18]										26.2 (7.8) 26.9 (8.2)		
Craig et al. 2020 [20-22]	Craig et al.Cohort 1 [21] Craig et al. Cohort 2 [21]			43.7 (8.9) 40.5 (9.7)	53.6 (10.1) 55.0 (10.7)	53.5 (9.3) 57.6 (10.1)			51.5 (9.7) 52.0 (10.5)		50.5 (8.9) 47.2 (10.2)	50.5 (8.3) 51.1 (9.7)	48.7 (8.8) 49.0 (9.4)
Gavigan et al. 2020[b] [23]				37.8 (34.0-40.8)	63.0 (58.7-67.9)	63.3 (60.3-66.9)			59.2 (54.3-63.0)				
Heisler et al. 2020 [24]		[m]										53.6 (8.9)	50.9 (9.1)
Hitchon et al. 2020 [25]												≥60[h] 24.0%	≥60[h] 22.7%
Hwang et al. 2020 [26]		45.6 (8.9)		46.6 (9.8)	51.1 (10.5)	52.2 (9.9)		45.7 (8.9)					45.3 (8.5)
Katz et al. 2020 [27]						56.3 (95)							
Liew et al. 2020 [28]												54.0 (9.0)	
Bingham et al. 2019 [30, 31]	Bingham et al. 2019 [30]		[m]	38.7 (9.4)	58.0 (11.6)[c] 58.0 (11.5)[d] 58.6 (11.6)[e]				53.9 (10.0)		44.8 (10.3)[j]	52.9 (10.1)	51.5 (10.5)
Crins et al. 2019 [32, 33]	Crins et al. 2019 [32]					53.6 (9.8)	56.7 (5.1)						

Table 3 (continued) T-scores (SD) of PROMIS measures in populations with axSpA and RA.

Study and articles within the study reporting T-scores	Articles or cohorts within the study Reporting PROMIS outcome	GH	P-29	Physical Function	Fatigue	Pain IF	Pain BH	Pain IT	Sleep Disturbance/ Sleep-Related Impairment[i]	Satisfaction with Social Roles and Actitvities	APS	Anxiety	Depression
Izadi et al. 2019 [34]				40.1 (10.7)									
Mahmoud et al. 2019 [35]				37.6 (6.9)	59.3 (5.9)	61.1 (5.5)		53.6 (5.5)	54.6 (3.7)			59.9 (6.0)	57.7 (8.3)
Wohlfahrt et al. 2019 [36]		41.4 (7.3)[k] 48.0 (8.2)[l]			56.8 (8.6)[c]	60.6 (7.3)	59.2 (4.7)	51.5 (6.0)	55.2 (9.8)[j] 55.2 (8.5)			54.3 (8.8)	50.8 (9.7)
Bartlett et al. 2018 [30, 38]	Bartlett et al. cohort 1 [38] Bartlett et al. cohort 2 [38] Bartlett et al. cohort 3 [38]				54.8 (13.6)[d] 54.6 (11.2)[e] 65.6 (8.1)[d] 66.0 (7.8)[e] 53.2 (9.9)[d] 55.3 (10.3)[e]								
Katz et al. 2018 [39]					59.3 (6.7)	60.9 (7.3)							
Bacalao et al. 2017 [41]				42.3 (5.9)	56.4 (9.2)	57.6 (7.5)							51.4 (8.4)
Katz et al. 2017 [42]			[m]	42.0 (9.1)	53.6 (11.0)	56.4 (9.4)			51.2 (9.3)	48.9 (9.7)		48.3 (9.2)	47.8 (8.7)
Wahl et al. 2017 [43]				40.2 (10.5)									
Askew et al. 2016 [44-47]	Askew et al. 2016 [44][a] Cella et al. 2015 [45] Beaumont et al. 2021 [46] Schalet et al. 2016 [47][a]			 40.7 (9.0) 40.7 (39.9-41.5)	 53.8 (8.8)[b] 53.7 (8.8)[g]	55.3 (54.6-56.0) 55.2 (8.6)							
Fries et al. 2011 [52-54]	Fries et al. 2011 [53]				33.9 (22.0)[f] 30.6 (21.0)[g]								

APS Ability to Participate in Social Roles and Activities; axSpA axial spondyloarthritis; GH Global Health; Pain BH Pain Behavior; Pain IT Pain Intensity; Pain IF Pain Interference; P-29 PROMIS-29; RA rheumatoid arthritis; SD standard deviation.

[a] Mean (95% Confidence Interval). [b] Median (Interquartile range). [c] 4-items. [d] 7-items.

[e] 8-items. [f] 10-items. [g] 20-items. [h] Outcome was not a T-score but a percentage of the population of a certain T-score.

[i] PROMIS Sleep Disturbance unless stated otherwise. [j] PROMIS Sleep Related-Impairment. [k] PROMIS Physical Global Health.

[l] PROMIS Mental Global Health. [m] General Questionnaire was used, but only sub scores were reported.

Discussion

This systematic literature review on the use of PROMIS measures in clinical studies in RA and axSpA patients identified 29 studies described in 40 articles. In total, two general health and 13 domain-specific PROMIS measures were used, with the PROMIS Pain interference, Fatigue, and Physical function and Depression being the measures that were most often reported. Overall, there was considerable variety concerning the versions of PROMIS measures that were used.

The 29 included studies were published from 2011 up to 2022, with relatively more articles published in recent years. As the total number of publications on clinical studies in RA and axSpA has also grown markedly, it remains to be ascertained whether the proportion of studies using PROMIS measures as outcome measures increased with time. Overall, the total number of identified studies using PROMIS measures is quite small as compared to the wealth of clinical studies in inflammatory arthritis published in the past two decades.

Regarding the nature of the PROMIS measures that were identified, most of the measures cover dimensions as described in the International Classification of Functioning, Disability and Health (ICF) Core Sets (Comprehensive and Brief) for Rheumatoid Arthritis and for Ankylosing Spondylitis [56, 57]. Similarly, the full range of measures is in line with the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) recommendations for outcome assessment in RA and axSpA patients in clinical trials [58, 59]. Both the ICF Core sets and OMERACT recommendations include health domains rather than specific measurement instruments, such as PROMIS measures. Specific measures are included in the more recently developed ICHOM core set for inflammatory arthritis, which particularly advocates the use of PROMIS measures, i.e., the PROMIS General Health, PROMIS Pain Interference, PROMIS Physical Function and PROMIS Fatigue measures [13]. In line with the ICHOM core set, we found that these were the PROMIS measures that were most often used. However, there was also substantial use of other PROMIS measures that were not recommended by ICHOM, such as the PROMIS Sleep Disturbance, PROMIS Abilities to Participate in Social Roles and Activities, PROMIS Depression and PROMIS Anxiety. Although not advocated by ICHOM, they do concern the domains as proposed by the OMERACT recommendations and the ICF core sets. It is unclear so far if the use of measures covering areas such as sleep indicates that the content of some established core sets must be revised. Moreover, the use of PROMIS measures also depends on the research

question to be answered. Hence some studies warrant the use of not recommended PROMIS measures and within such studies the recommended PROMIS measures may be less relevant. With respect to the actual scores of the PROMIS measures, the T-scores extracted from 21 studies were generally in line with the expectation that patients with RA and axSpA have a worse health status than the general population. There were, however, some exceptions where the T-scores indicated better health than expected, namely in the Depression and Abilities to Participate in Social Roles and Activities. Overall, the number of T-scores available per PROMIS measure was low, and often different versions of an instrument were used. Of note is that we observed considerable variation regarding the versions of specific PROMIS measures that were used. Although this could in part be explained by the launch of updates, there was also quite some variation regarding the number of items and the naming. It remains to be established if comparisons of scores where different versions of one measure have been used are valid. Therefore, taking the latter into account as well as the variation in the number of items and the naming of the PROMIS measures, we could not conduct subgroup analyses. Hence, conclusions on the level of T-scores for RA and axSpA patients cannot be drawn.

This study had some limitations that need to be addressed. First, as a result of the large diversity of the included studies in terms of follow-up moments, presentation of the data, and inclusion criteria, we did not yet review the data on psychometric properties of PROMIS measures according to the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) guidelines. Second, the large variability between studies also hampered the further comparison between populations and studies in terms of a meta-analysis. Third, the limited amount of four studies reporting on axSpA patients (3 studies reported solely on axSpA, one study reported on RA and axSpA patients) compared to the 25 studies solely on RA patients which hampered the interpretation for the axSpA patient group. Subsequently, we were unable to compare these two groups together and we displayed the individual data and analyzed the total data of the RA patients and axSpA patients combined. Finally, the possible overrepresentation of the use of certain PROMIS measures as a result of studies that were based on similar populations. Some studies showed overlap with others but were considered as a separate study since the data were not exactly the same in terms of the sample sizes and general patient characteristics.

Nevertheless, the broad eligibility allowed the inclusion of most of the relevant literature,

thereby presenting a fairly complete picture of the use of PROMIS measures in clinical research in inflammatory arthritis. The conduct of the study according to the PRISMA recommendations supports the accuracy and validity of the work.

In conclusion, currently, PROMIS measures are not often used in clinical studies in patients with RA and with axSpA. Within the studies that did use them considerable variety regarding the different PROMIS measures used as well as the specific versions of each instrument was present. As expected, the PROMIS measure outcomes depicted the overall impaired health outcomes in RA and axSpA populations. In future research, to facilitate comparisons across studies, more standardization regarding the use of PROMIS measures in clinical studies in RA and axSpA is needed.

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Author Contributions

TPMVV and MGJG and JWS contributed to the study conception and design. Acquisition of data was performed by JWS, MMHT, IREK, TPMVV, and MGJG. The analysis and interpretation of the data were performed by MMHT, IREK, SFEvW, CHMvdE, TPMVV, and MGJG. The first draft of the manuscript was written by MMHT, MGJG, and TPMVV, and all authors commented on this first draft by revising later versions of the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Ethical approval and consent to participate

Statements regarding informed consent or ethical approval were not applicable to this article as it is a systematic review.

Supplemental files

- Supplementary file 1: Search strategy.

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Supplemental files

Supplementary file 1 Search strategy.

PubMed
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"Marie Struempell Disease" OR "Marie Struempell Disease" OR "Rheumatoid Spondylitis" OR "Spondyloarthritis Ankylopoietica" OR "Spondylarthritis" OR "Spondylarthrit*" OR "Spondylarthr*" OR "Spondylarthropathy" OR "Spondylarthropathies" OR "Spondylarthropathy" OR "Spondylarthr*" OR "Sacroiliitis" OR "Sacroiliitis" OR "Sacroiliit*") AND TI("PROMIS" OR "PROMIS10" OR "NIHPROMIS" OR "PROMISPI" OR "PROMISPF" OR "PROMISGH" OR "PROMISSF" OR "Patient Reported Outcome Measurement Information System" OR "patient reported outcome measurement system" OR "Patient Reported Outcomes Measurement Information System" OR "patient reported outcomes measurement system")) **OR** (KW("Inflammatory Arthritis" OR "Rheumatoid Arthritis" OR "Rheumatoid Arthritis" OR "RA" OR "Caplan Syndrome" OR "Felty Syndrome" OR "Rheumatoid Nodule" OR "Rheumatoid Vasculitis" OR "Sjogren's Syndrome" OR "Sjoegren's Syndrome" OR "Sjogren Syndrome" OR "Sjoegren Syndrome" OR "Sjogrens Syndrome" OR "Sjoegrens Syndrome" OR "Sjogren's Syndrome" OR "Adult Onset Still's Disease" OR "Adult Onset Stills Disease" OR "Spondyloarthritis" OR "axial spondylarthritis" OR "axial spondylarthrit*" OR "axial spondyloarthritis" OR "axial spondyloarthrit*" OR "AxSpA" OR "ankylosing spondylitis" OR "Ankylosing Spondylarthrit*" OR "Ankylosing Spondylarthritis" OR "Ankylosing Spondylit*" OR "Ankylosing Spondyloarthrit*" OR "Ankylosing Spondyloarthritis" OR "Bechterew Disease" OR "Bechterews Disease" OR "Bechterew's Disease" OR "Marie Struempell Disease" OR "Marie Struempell Disease" OR "Rheumatoid Spondylitis" OR "Spondyloarthritis Ankylopoietica" OR "Spondylarthritis" OR "Spondylarthrit*" OR "Spondylarthr*" OR "Spondylarthropathy" OR "Spondylarthropathies" OR "Spondylarthropathy" OR "Spondylarthr*" OR "Sacroiliitis" OR "Sacroiliitis" OR "Sacroiliit*") AND TI("PROMIS" OR "PROMIS10" OR "NIHPROMIS" OR "PROMISPI" OR "PROMISPF" OR "PROMISGH" OR "PROMISSF" OR "Patient Reported Outcome Measurement Information System" OR "patient reported outcome measurement system" OR "Patient Reported Outcomes Measurement Information System" OR "patient reported outcomes measurement system"))

Google Scholar
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(first 10 items selected)
"Patient Reported Outcome Measurement Information"|"patient reported outcome measurement system"|"Patient Reported Outcomes Measurement Information"|"Patient Reported Outcomes Measurement Information" "Rheumatoid Arthritis"
(first 10 items selected)
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(first 10 items selected)
"Patient Reported Outcome Measurement Information"|"patient reported outcome measurement system"|"Patient Reported Outcomes Measurement Information"|"Patient Reported Outcomes Measurement Information" "ankylosing spondylitis"|"Sacroiliitis"
(first 10 items selected)
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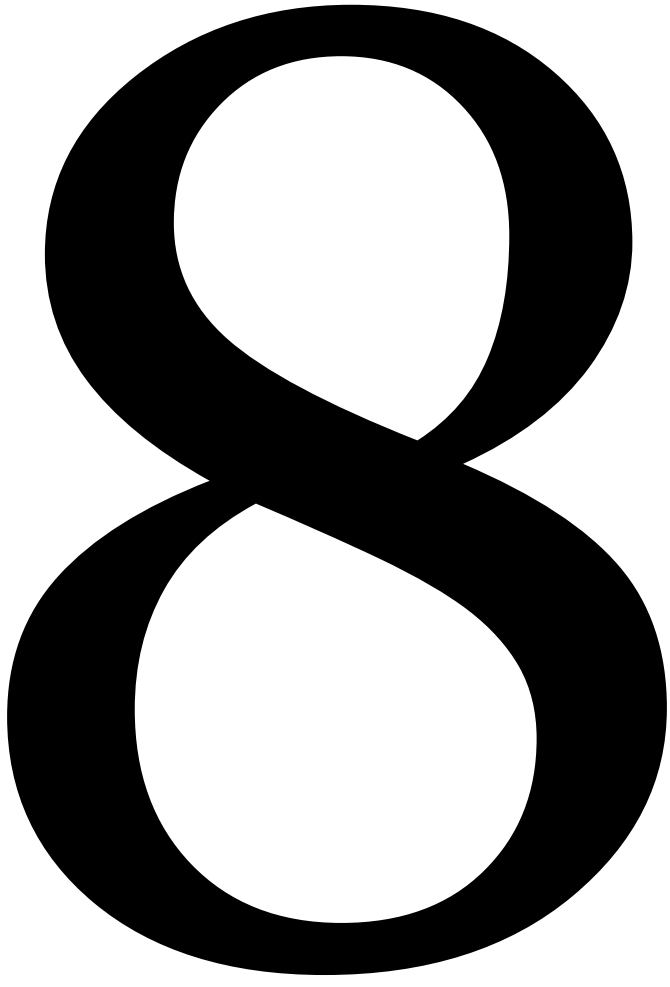
(first 40 items selected)



Chapter 8

Quality of reporting and nature of harms in clinical trials on supervised exercise in patients with rheumatoid arthritis or axial spondyloarthritis

Max M.H. Teuwen[1], Thea P.M. Vliet Vlieland[1], Salima F.E. van Weely[1], Jan W. Schoones[2], Anne-Kathrin Rausch Osthoff[1,3], Carsten B. Juhl[4,5], Karin Niederman[3], Maaike G.J. Gademan[1,6], Cornelia H.M. van den Ende[7,8]

1. Department of Orthopaedics, Rehabilitation and Physical Therapy, Leiden University Medical Center, Leiden, The Netherlands;
2. Directorate of Research Policy, Leiden University Medical Center, Leiden, The Netherlands;
3. School of Health Sciences, Institute of Physiotherapy, Zurich University of Applied Sciences, Winterthur, Switzerland;
4. Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark;
5. Department of Physiotherapy and Occupational Therapy, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark;
6. Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands;
7. Department of Research, Sint Maartenskliniek, Nijmegen, The Netherlands;
8. Department of Rheumatology, Radboud University Medical Center, Nijmegen, The Netherlands.

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Abstract

Objectives: To describe the quality of reporting and the nature of reported harms in clinical studies on the effectiveness of supervised exercises in patients with rheumatoid arthritis (RA) or axial spondyloarthritis (axSpA).

Methods: We performed a systematic review, searching eight databases up to February 2023. Randomized controlled trials (RCTs) evaluating supervised exercises in adults with RA or axSpA were considered eligible. Data on harms were extracted according to the CONSORT Harms 2022 Checklist. Among others, it was recorded if harms were prespecified or non-prespecified. Moreover, the nature of reported harms was listed.

Results: Forty RCTs were included for RA and 25 for axSpA, of which 29 (73%) and 13 (52%) reported information on harms. In 13 (33%) RCTs in RA and four (16%) in axSpA, the collection of harms outcomes was described in the methods section. Prespecified outcomes were reported by eight (RA) and two (axSpA) RCTs. Non-specified harms outcomes were reported by six (RA) and four (axSpA) RCTs. Prespecified harms outcomes included measures of pain, disease activity, inflammation, and structural joint changes. The nature of non-prespecified harms outcomes varied largely, with pain being most common. A considerable proportion of trials on supervised exercise in RA or axSpA does not or inadequately report harms outcomes. Pain was the most commonly reported prespecified or non-specified harm.

Conclusion: For a considerate interpretation of the balance between benefits and harms of supervised exercise in RA or axSpA, use of the CONSORT Harms 2022 Checklist for the design, conduct and reporting of trials is advocated.

Keywords: Systematic review; Safety; Exercise therapy; Rheumatoid arthritis; Axial spondyloarthritis.

Introduction

Exercise therapy is a generally proven effective intervention for people with rheumatic and musculoskeletal diseases (RMDs), including those with inflammatory arthritis, such as rheumatoid arthritis (RA) [1, 2], axial spondyloarthritis (axSpA) [3, 4], or both [5]. The reported beneficial effects of exercise therapy in patients with RA or axSpA include improvement of aerobic capacity, muscle strength, and/or overall functional ability, as well as a decrease in pain [1–5]. As such, exercise therapy is included in professional recommendations for the management of RA [6] and axSpA [7]. Despite the documented benefits of exercise therapy, the occurrence of undesired effects, i.e., harms, is also plausible, as exercise therapy could potentially lead to (muscle) pain, exertion, an increase of local or general disease activity or joint damage [8], or to exercise-related injuries. Indeed, anticipated harms or a lack of knowledge on this aspect was found to be barriers for patients to engage in exercise therapy and for professionals to advise or provide it [9, 10]. Previous systematic reviews on the effectiveness of exercise therapy in RA or axSpA concluded that exercise therapy is likely to be safe, although it was noted that safety was scantly described in the selected trials. Indeed, it was noted that there is only a relatively small proportion of trials reporting on any harms outcomes. To advise patients, a thorough insight in the balance between benefits and harms of supervised exercise is needed. For a correct interpretation, it is crucial that both benefits and harms of exercise therapy are adequately documented.

The poor reporting of harms in randomized controlled trials on non-pharmacological care in RMDs was already acknowledged years ago [11]. However, only recently, systematic reviews specifically investigated the potential harms of exercise therapy, based on trials in patients with various conditions including RMDs [12] and osteoarthritis (OA) specifically [13, 14]. The systematic review by Niemeyer et al. [12] included 773 primary trials, 41 of which were done in people with RMDs. They found no increase in risk of serious adverse events (SAEs), but an increase in the risk of non-SAEs related to exercise therapy, concluding that exercise therapy can be recommended as a relatively safe intervention. The two systematic reviews on adverse events (AEs) in hip or knee OA focused on the reporting of harms [13, 14]. It was found that in less than 50% of the 113 trials in knee OA [13] and 14 in hip OA [14], a statement on AEs was included.

The insufficient reporting of harms in trials on exercise therapy is striking as the Consolidated Standards of Reporting Trials (CONSORT) extension for randomized trials of non-pharmacologic treatments, in 2008 [15] and updated in 2017 [16] explicitly mentions the reporting of all important harms or unintended effects in each group. Herewith, it refers to the CONSORT extension for the reporting of harms, first published in 2004 [17] and updated recently [18]. Consistent with the previous version, in the CONSORT Harms 2022 statement, harms are defined as the opposite of benefits, i.e., the totality of possible adverse consequences of an intervention. Key elements of the 2022 update are the distinction between pre-specified and non-specified harms, and the systematic and the non-systematic assessment of harms (i.e., passive or unstructured reporting of harms such as the unprompted self-reporting by participants).

In summary, there is a growing interest in the reporting of harms in trials on exercise therapy in RMDs, yet insight in the quality of reporting and the nature of harms outcomes in trials on the effectiveness of exercise therapy in RA or axSpA is limited. The availability of updated guidelines on the appropriate reporting of harms may help elucidate the areas where the reporting is specifically inadequate. More insights into the specific weaknesses may help improve not only the reporting but also the design and conduct of exercise therapy trials in this field. In addition, insight in the nature of reported harms outcomes might facilitate the development of structured assessments of harms to be used in future trials on the benefits and harms of exercise therapy. The aims of this systematic literature review are to investigate the quality of reporting on harms outcomes and to describe the nature of reported harms outcomes in studies on the effectiveness of exercise therapy in RA or axSpA patients.

Methods

Study design

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and MetaAnalysis (PRISMA) statement using those items that were relevant for the research questions in our study [19]. Our study protocol was registered in PROSPERO, an International prospective register of systematic reviews (registered August 29, 2020). Otherwise than described in our study protocol, we decided to restrict our review to studies on the effectiveness on supervised exercise therapy in RA or axSpA, considering two recent systematic reviews about reporting harms outcomes in knee and hip OA [13, 14].

Search strategy

Eligible studies were identified through an search strategy that was developed by a trained librarian (JS) and employed in a previous systematic review [5] on the effectiveness of exercise therapy and physical activity interventions in RA, axSpA, and knee and hip osteoarthritis (April 2017) (see Supplementary Appendix 1). For the current systematic review, the search was extended with search terms for harms, such as AEs or risk. The final search was performed on February 6, 2023.

The search strategy was developed for PubMed/Medline, using MeSH terms and free text, and then modified for use in Embase (OVID), Web of Science, Emcare (OVID) and PsycINFO (EbscoHOST), Academic Search Premier (EbscoHOST), PEDro, and the Cochrane Library (see Supplementary Appendix 1 for the search strategy details for all databases). This search was intentionally broad with no language or other restrictions being set in order not to miss any potentially relevant studies. The identified records were imported into an application enabling independent selection of publication by multiple reviewers, Rayyan (http://rayyan.qcri.org) by one of the researchers (JS) and duplicates were removed before the start of the study selection [20].

Selection criteria

We included randomized controlled trials (RCTs) comparing an exercise therapy intervention (aerobic, muscle strengthening, range of motion or flexibility, neuromotor (including balance exercises), stretching, or mind–body exercises) with at least six sessions being supervised by a qualified health care professional with a control condition. This criterion of a minimum of six sessions being supervised was deemed appropriate to exclude home-based interventions in combination with a limited number of face-to-face encounters with the therapist for instruction. We included studies that enrolled adult patients with a diagnosis of RA or axSpA and were published in the English language. The diagnostic process may involve clinical assessment or the application of specific classification criteria for RA or axSpA. In the context of axSpA, this approach encompasses both non-radiographic and radiographic forms of the condition. Trials on post-surgical exercise therapy or including patients with multiple diagnoses yet not reporting on RA and axSpA patients separately were not considered eligible. Moreover, studies with a randomized, cross-over design or with randomization on the level of institution (e.g., cluster randomized controlled trials) were excluded.

Selection of studies

The titles and the abstracts identified from the search were subsequently screened for eligibility. First, every record was screened with respect to the inclusion and the exclusion criteria by two of three reviewers (MT, CE, and TVV), independently. Second, the full-text papers of the potentially eligible records were retrieved and screened again independently by two of the three reviewers using the same eligibility criteria. In case a study was reported in multiple publications, information from these publications was taken into account. Publications were considered to be related to the same study based on sample size, recruitment site, general patient characteristics, and/or trial registration number if applicable. Any disagreements on the selection of studies were resolved by discussion among the three researchers.

Data extraction

Data were extracted from the selected studies using a standardized sheet (Supplementary Appendix 2). The data extraction sheet was pilot-tested, and subsequently data extraction from each study was independently performed by two of three reviewers (MT and either CE or TVV). Any disagreements were resolved by discussion among the three researchers. Data extraction was done in two steps, with different levels of detail.

Step 1: general study characteristics, reporting of any harms and details on harms reporting

First, from all the included studies, the following characteristics were extracted for studies on RA and axSpA separately: first author and year of publication, number of treatment arms, and number of patients per treatment arm. If a study was described in multiple papers, the information from the publications other than author and year of publication was combined and, with further references the oldest publication was used. Moreover, it was recorded if any information on harms was included in the publication (title and abstract, introduction, methods, results (including figures and/or tables), or discussion). For that purpose, multiple terms that were used by authors to label harm outcomes were taken into account, including e.g., harms, side effects, negative effects, AEs, safety, and risk. In addition, outcomes pain, disease activity, inflammation, or radiologic joint damage was considered as potential harms outcomes, but only if the authors explicitly designated these as such in the publication. The same strategy was employed for information on reasons for drop-outs.

In addition to the abovementioned six items recording the presence of any information in specific parts of the publication(s), information on harms outcomes was further extracted using a selection of eight harms-related items from the CONSORT Harms 2022 checklist [18]. The selection of these items was based on their relevance to the specific intervention, i.e., supervised exercise therapy. Thus, in line with the updated and previous version of the CONSORT Harms extension [17, 18], it was recorded whether a hypothesis or study objective regarding harms was formulated.

With regard to data collection, we recorded whether the method and the timing of prespecified and non-prespecified harms outcomes were described and whether active (i.e., collection of harms outcomes by actively asking or assessing) or passive (i.e., collection of harms outcomes by relying on the spontaneously report by study participants or supervisors of exercise therapy) surveillance had taken place [18]. Regarding the results, it was furthermore extracted from the studies whether or not details (timing, duration, or severity) on harms outcomes were presented, and whether the observation of no harms was underpinned by the report on zero events. Finally, for the discussion, it was recorded if a reflection on harms rather than just their mentioning was presented.

Step 2: detailed study characteristics and harms outcomes of a further selection of studies
Second, additional data on the study characteristics (content of intervention and control conditions, intervention duration) and the nature of assessed of harms were extracted in those papers that presented information on harms outcomes in the methods section(s). The rationale for this selection of papers was that, according to the CONSORT Harms checklists, the quality of reporting is mainly determined by the description of the methodology for the ascertainment of harms [17, 18].

Statistical analysis and synthesis

Descriptive analyses were used for the analyses of the extracted information. For each of the 14 items of the list on quality of reporting harms, the proportions of studies meeting that criterion were calculated.

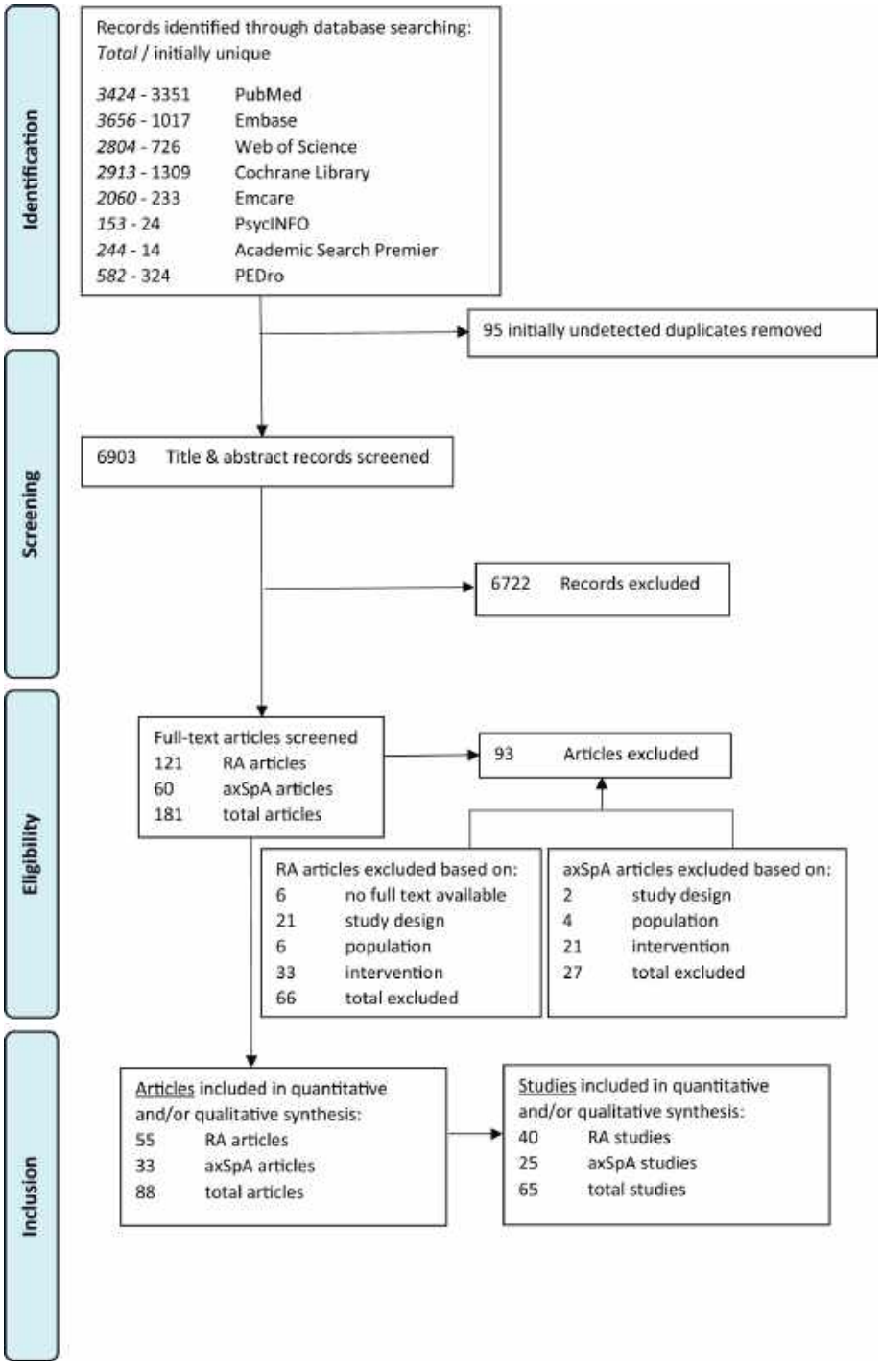
Moreover, any text passages concerning harms outcomes were systematically gathered and documented for studies including relevant information in either the methods or results sections of the manuscript. To ensure data accuracy, the analyses were conducted by MT and checked by CE.

Results

Study selection

The search identified a total of 6903 records. A total of 6722 records were excluded during the initial screening on title and abstract (Fig. 1), with the study pertaining to patients with OA, the intervention not being supervised exercise therapy or a non-randomized study design being the main reasons for exclusion. Of the remaining 181 records, the full-text papers were retrieved. Using the same eligibility criteria, 55 papers reporting on 40 RCTs in RA and 33 papers reporting on 25 RCTs in axSpA were finally included. The characteristics of the 65 selected RCTs and the references to the publications in which they are described are presented in a supplemental table (Supplemental Table 1). From these, the numbers (proportions) of RCTs published in the past 10 years (2013–2023) were 19 (48%) and 19 (76%) in RA and axSpA, respectively.

Figure 1 Flowchart search strategy and screening process.



Quality of reporting on harms

Table 1 shows the quality of reporting about harms outcomes for the 65 selected studies. Most of the included studies reported harm-related information in one or more sections of the manuscript(s): 29 (73%) and 13 (52%) of RCTs in RA and axSpA, respectively.

Title and/or abstract

In 10 (25%) and five (20%) of the studies in RA and axSpA, respectively, harms were addressed in the title and/or the abstract [21–35]. In about half of the cases, this included a specific hypothesis or research aim on harms.

Introduction

Fifteen of the 40 (38%) RA studies and four (16%) of the axSpA studies addressed the issue of harms in the introduction section of the manuscript. A minority of studies (eight (20%) of RA and two (8%) of axSpA studies) included harms outcomes in their objectives [21, 22, 25–30, 36, 37].

Methods

In 13 (33%) of the RA studies and four (16%) of the axSpA studies, the data collection on harms outcomes was described in the methods section [21, 22, 25–32, 36–42]. Of these, eight (20%) of the RA and two (8%) of the axSpA studies reported prespecified harms outcomes [21, 22, 26, 27, 29, 31, 32, 36, 37, 42]. None of the included studies used a prespecified threshold of these outcomes to determine their occurrence in individual patients, but rather evaluated changes in these outcome measures over time on the group level. Systematic assessment of non-prespecified harms outcomes by means of active surveillance was described in two (5%) RA and one (4%) axSpA studies [38–40]. Active surveillance comprised a planned physical examination by a rheumatologist [38], regular structured assessment of AEs by a nurse [39], or a training diary for the experimental group and a two-weekly assessment of AEs in the control group by phone [40]. Reported methods of passive surveillance comprised asking participants to report to the trial personnel if any AEs occurred [32, 41] or just mentioning that AE were recorded [25, 28–30, 42], and in one of these, a reference to the 2004 CONSORT statement on harms was made [28].

Results and discussion

Information on harms outcomes was included in the results sections (including figures and/or tables) of 18 (45%) of the RA and nine (36%) of the axSpA studies and in the discussion sections of 24 of the RA studies (60%) and eight of the axSpA studies (32%). In some studies, results on harms were only reported in the discussion section [43, 44], whereas some other studies only concluded that the examined intervention was safe without presenting any data [33, 45–47].

Table 1 Quality of reporting of harms outcomes in studies on the effectiveness of supervised exercises in RA and axSpA.

Item description[a]		RA (N=40) yes, N (%)	axSpA (N= 25) yes, N (%)
1	**Harms-related information anywhere in the manuscript?**	29 (73)	13 (52)
2	**Harm-related information in the title and/or abstract?**	10 (25)	5 (20)
3	**Harms outcomes in the introduction?**	15 (38)	4 (16)
	• Specific objectives or hypotheses for harms outcomes?	8 (20)	2 (8)
4	**Information on data collection of harms outcomes in the methods?**	13 (33)	4 (16)
	Prespecified harms outcomes:		
	• Method and timing of assessment described?	8 (20)	2 (8)
	Non-prespecified harms outcome:		
	• Method and timing of systematic assessment (active surveillance[b]) of harms outcomes described?	2 (5)	1 (4)
	• Method of passive surveillance of harms outcomes described?	4 (10)	3 (12)
5	**Information on harms outcomes in results section (including figures and/or tables)?**	18 (45)	9 (36)
	• Reported details on prespecified harms outcomes?	8 (20)	2 (8)
	• Reported details (timing, duration or severity) on non-prespecified harms outcomes?	4 (10)	0 (0)
	• Reported information about the number of observed AEs?	16 (40)	7 (28)
6	**Harms-related issues or information in discussion?**	24 (60)	8 (32)
	• Reflection on findings on harms of the study?	19 (48)	2 (8)

Items are derived from the CONSORT Harms statement 2022 [18].
AE adverse event; RA rheumatoid arthritis; axSpA axial spondyloarthritis.
[a] References of all included studies can be found in Supplementary Table 1.
[b] Description of data collection adverse events in the methods section by actively asking or evaluating whether an adverse event occurs.

Nature of harms

Table 2 presents the characteristics of the intervention and the nature of harms, of the 17 studies providing sufficient information on the methodology of ascertainment of harms in the methods section. The interventions evaluated in these studies consisted mainly of aerobic and/or muscle strengthening exercises and/or stretching exercises and/or walking exercises, with the exception of one study on hand exercises [32] and one on Tai Chi [25] in RA and one study on Baduanjin Qigong training [30] in axSpA.

Prespecified harms

The description of the methodology for the ascertainment of harms comprised prespecified harms outcomes in the methods section in eight of the 13 selected studies in RA [21, 22, 26, 27, 31, 32, 36, 37] and two of the four studies in axSpA [29, 42]. Prespecified harms predominantly concerned measures of disease activity, pain, and/or biological markers for inflammation. Three studies reported prespecified harms outcome with respect to structural changes (radiographic damage on X-rays, deformity of metacarpal phalangeal joints) [21, 31, 32]. In two studies in axSpA, both from the same author [29, 42], the measurement of harms was described on the individual patient level (absence of a fare-up in disease activity and was defined in terms of stable or decreased self-reported disease activity and acute phase reactants).

Non-prespecified harms

In RA, in six of the 13 selected studies [25, 28, 32, 38, 40, 41], the collection of information on non-prespecified harms was reported. In one study, this was done in combination with the collection of prespecified harms [32]. In two of these six studies [38, 40], active surveillance and in four other passive surveillance were employed. In axSpA, in all four studies reporting on harms outcomes in the methods section [29, 30, 39, 42], the collection of non-prespecified harms was reported. In two of these studies [29, 42], this was combined with the collection of prespecified harms. In one of these four studies [39], active surveillance and in three passive surveillance were reported. In the five studies reporting on AEs in the intervention group [25, 29, 30, 38, 41], the nature of the following types of non-prespecified AEs in the intervention group was reported: musculoskeletal pain, joint swelling, flare-up, nausea, flu/cold/influenza (more than one study); fall, neuralgia, surgery, morning stiffness, low back pain, hypertension, chest infection, and chest pain (one study).

Table 2 Description of the methods of collection and nature of harms outcomes and observed results of those studies reporting the collection of harms outcomes in the methods section.

Author and publication year	Description of study arms	Duration intervention (weeks)	Prespecified harms outcomes		Non-prespecified harms outcomes	
			Method of collection of harms outcomes	Results on harms outcomes	Method of collection of harms outcomes	Results on harms outcomes
Rheumatoid arthritis (N=13)						
Mckenna et al. 2021 [41]	Walking-based exercise (n=12); Advice on the benefits of exercise (n=12)	8	-	-	*Passive surveillance* Participants were advised to seek medical assistance if there was AEs during the intervention e.g. flareup, fall, or if the participant feels unwell. Primary safety outcomes included the type and frequency of AEs	No SAEs related to the intervention. Nature of AEs reported: Musculoskeletal pain (intervention and control groups), RA flare-up (intervention and control groups), nausea (intervention and control groups), cold/flu (intervention and control groups), chest infection (intervention and control groups), fall (intervention and control groups).
Ward et al. 2018 [28]	Group and home-based yoga (n=13); Usual care (n=13)	8	-	-	*Passive surveillance* Primary safety outcomes included the type and frequency of AEs (Ioannidis et al., 2004).	No SAEs were related to the study. AEs reported: musculoskeletal pain (intervention and control groups), nausea (intervention group), RA flare-up (intervention and control groups), flu (intervention and control groups), neuralgia (intervention and control groups),surgery(intervention and control groups), infection (control group).
Siqueria et al. 2017 [38]	Water-based (WB) exercise (n=33); Land-based (LB) exercise (n=33); No (C) exercise (n=34)	16	-	-	*Active surveillance* The recording of concomitant medications and AEs was performed every 8 weeks by the rheumatologist during the clinical evaluations. For the definition of AE and SAEs international recommendations were followed.	SAEs during intervention period: Cerebrovascular accident (LB), death (LB). AEs during intervention period: Worse due to pain or joint swelling (LB and C), depression (C), morning stiffness (WB, LB, C), low back pain (WB, LB, C), nonrestorative sleep (C), hypertension (WB, LB), influenza (WB).
Lamb et al. 2015 [32, 55-57][a]	Hand exercise program (n=246); Usual care (n=244)	12	Disease activity measures (N of tender and swollen joints, degree of joint deformity of MCP joints scored at baseline, 4 and 12 months)	No differences between groups	*Passive surveillance* SAEs (death, life threatening events, hospitalization, medical intervention, and disability) and AEs reported by clinicians, researchers, or participants were recorded by therapists, research clinicians or participants and classified as related, unrelated, and possibly related to treatment.	SAEs were reported, but none were regarded as related to treatment: Death (control group), life-threatening condition (Intervention and control group) , hospital admission (Intervention and control groups), needing medical intervention (Intervention and control groups), disability accounted for by flares of RA (Intervention and control groups), transient exacerbation of arm pain (intervention group).

Table 2 (continued) Description of the methods of collection and nature of harms outcomes and observed results of those studies reporting the collection of harms outcomes in the methods section.

Author and publication year	Description of study arms	Duration intervention (weeks)	Prespecified harms outcomes		Non-prespecified harms outcomes	
			Method of collection of harms outcomes	Results on harms outcomes	Method of collection of harms outcomes	Results on harms outcomes
Strasser et al. 2011 [27]	Strength and endurance training (n=20); Stretching exercises (n=20)	26	Measures of disease activity (laboratory markers (CRP, ESR), medication, DAS, pain), assessed after intervention.	No changes in ESR and CRP. Disease activity and pain decreased in intervention group	-	-
Hsieh et al. 2009 [26]	Supervised aerobic exercise (n=15); Home-exercise (n=15)	8	Severity and extent of arthritis (pain, physician global assessment, laboratory tests), assessed before and after intervention.	Intervention group improved in pain and disease activity; no differences between groups.	-	-
Wang et al. 2008 [25]	Tai Chi exercises (n=10); Stretching & wellness education (n=10)	12	-	-	*Passive surveillance* AEs were recorded.	There were no AEs associated with Tai Chi or education and stretching training during the 12-week study period.
De Jong et al. 2003 [21, 59-63][a]	Supervised group exercise (n=158); Usual care (n=151)	104	Primary end point of safety was radiographic damage of the large joints (at 12 and 24 months), secondary end point was disease activity (DAS) assessed every 3 months by blinded assessors.	No difference in radiographic damage between groups; but a trend towards more damage in the intervention group was observed. Decrease in disease activity in both groups.	-	-
Van den Ende et al. 2000 [22]	Intensive exercise program (n=34) ; Conservative exercise program (n=30)	4	Disease activity (number tender of swollen joints, ESR, pain, evaluated at admission, 3, 6, 12 and 24 weeks after admission by blinded assessor.	Decline in disease activity measures in both groups, no significant differences between groups. Pain at 3 weeks was higher in intervention group.	-	-

Table 2 (continued) Description of the methods of collection and nature of harms outcomes and observed results of those studies reporting the collection of harms outcomes in the methods section.

Author and publication year	Description of study arms	Duration intervention (weeks)	Prespecified harms outcomes		Non-prespecified harms outcomes	
			Method of collection of harms outcomes	Results on harms outcomes	Method of collection of harms outcomes	Results on harms outcomes
Lyngberg et al. 1994 [37]	Progressive interval training (n=12); No training (n=12)	12	46 joints were examined for soft tissue swelling, tenderness, and pain during motion and laboratory assessments (ESR); assessed by rheumatologist 2 weeks before and after training.	Insignificant changes in disease activity in both groups, but number of swollen joints decreased significantly in intervention group.	-	-
Baslund et al. 1993 [36]	Physical training program (n=9); no training (n=9)	8	Monokines, ESR, CRP	No increases observed	-	-
Hansen et al. 1993 [31]	Self-training (n=14); Training in physiotherapy practice (n=14); Group training (n=14); Group training + Pool (n=13); No training (n=13)	104	Duration of morning stiffness, number of swollen joints , joint pain, medical treatment, ESR; assessed by physician every 3 months. X-ray every 12 months.	No statistical differences between groups	-	-

Table 2 (continued) Description of the methods of collection and nature of harms outcomes and observed results of those studies reporting the collection of harms outcomes in the methods section.

Author and publication year	Description of study arms	Duration intervention (weeks)	Prespecified harms outcomes		Non-prespecified harms outcomes	
			Method of collection of harms outcomes	Results on harms outcomes	Method of collection of harms outcomes	Results on harms outcomes
Axial spondyloarthritis (N=4)						
Sveaas et al. 2019 [29, 64-66][a]	High-intensity aerobic and strength exercises (n=50); Usual care (n=50)	12	Safety was considered as absence of disease flare-ups after the intervention period, defined as stable or decreased disease activity assessed by ASDAS, BASDAI, CRP, and ESR.	All measures (except CRP and ESR) improved statistically significant in favor of the intervention group.	*Passive surveillance*: AEs reported by the physiotherapists.	AEs reported during exercise in intervention group: -Chest pain and nausea -Persistent pain
Xie et al. 2019 [30]	Baduanjin qigong training (n=30); No training (n=30)	12	-	-	*Passive surveillance* All AEs were required to be recorded and reported to the researchers in the intervention and control group.	No SAEs were reported by the patients during the observation period. Patients in the Baduanjin qigong group reported mild muscle ache in the thigh and crus during the first two weeks of treatment.
Fang et al. 2016 [39]	Supervised exercise & home-based exercise (n=24); Home-based exercise (n=20)	26	-	-	*Active surveillance* Patients were followed up by telephone by a nurse every two weeks to complete questions on outcomes including AEs	Not described
Sveaas et al. 2014 [42, 67][a]	Endurance and strength training (n=13) Usual care (n=15)	12	Safety was considered as absence of a flare up in disease activity defined as stable or decreased self-reported disease activity (ASDAS and BASDAI) and acute phase reactants (CRP and ESR).	Increase in ASDAS in two patients of the intervention group. On group level decrease in ASDAS in the intervention groups. No differences in CRP and ESR between groups	*Passive surveillance* The report of any AE was included in the definition of safety.	Explicit statement that no AEs were observed.

AE adverse event; ASDAS The Ankylosing Spondylitis Disease Activity Score; BASDAI The Bath Ankylosing Spondylitis Disease Activity Index; CRP C-reactive protein; DAS Disease Activity Score; ESR Erythrocyte Sedimentation Rate; MCP metacarpophalangeal joints; SAE Serious adverse event.

[a] Studies comprises of multiple articles. The main article that was first published was used and the other articles are referred to in the references.

Discussion

This systematic literature review found that about 50–75% of studies on the effectiveness of supervised exercise therapy in RA or axSpA included any information on harms outcomes in the related manuscript(s). Of these, the majority did not further specify how harms outcomes were defined or monitored. Thus, the majority of the RCTs on the effectiveness of supervised exercise therapy in RA or axSpA lacks detail and consistency of reporting on harms that is imperative to make an accurate evaluation of harms of exercise therapy. Consequently, considering the findings of our review, to date, there is too little information to allow firm conclusions about the absence or the presence of harms of supervised exercise therapy for patients with RA or axSpA.

The issue of poor quality of reporting harms outcomes is well recognized in the literature for pharmacological as well as non-pharmacological interventions in RMDs. Ethgen et al. [11] concluded already in 2005 that the reporting of harms in published randomized, controlled trials of pharmacologic and non-pharmacologic treatment for RA and hip or knee OA was suboptimal and that harms outcomes were less often described less in reports of non-pharmacologic as compared to pharmacologic treatment trials. More recently, two systematic reviews [13, 14] on harms outcomes of exercise therapy in hip and knee OA concluded that less than half of trials included a statement on harms outcomes, in which the proportion is even lower than those observed in the present study. The two latter reviews also concluded that in many trials, the reasons for dropping out were, if applicable, not classified as AEs. The recommendation of the CONSORT 2022 Harms to describe reasons and timing for discontinuation, including if related to participants experiencing harms, might overcome this omission in future.

Remarkably, the number of studies reporting on harms outcomes in the results or discussion sections exceeded the number of studies with harms-related information in the methods section, whereas only a few trials explicitly formulated one or more research questions on harms outcomes. This finding indicates that although authors have failed to address harms according to the reporting guidelines, they are well aware of the relevance of potential harms of exercise therapy. A possible explanation for this inconsistency in reporting on harms is that for some outcomes, exercise therapy can have both positive and negative effects, particularly with respect to disease activity and pain levels [48–51]. In many studies included in our review, the outcomes on disease activity or pain were well

defined and systematically assessed and presented, however without any reference to whether or not they were considered as harms outcomes. In all of these cases, the results were presented on group level. While this approach provides valuable information on the impact of exercise therapy either positive or negative, it is possible that it may mask or overlook episodes of increased disease activity or pain experienced by individual patients in all study arms as possible harm. These effects might have occurred during the trial period but were not adequately captured. To address this issue, it is advisable to establish predetermined thresholds for disease activity measures and pain levels that are considered unacceptable and should be labeled as harm outcomes [18]. By specifying these cut-of points in advance, researchers can better identify and report on any AEs experienced by individual participants during exercise therapy interventions.

In addition to the unclarity about the interpretation of outcomes that were well described and systematically evaluated but not specifically designated as harms outcomes, a number of studies provided results on non-prespecified AEs, but did not mention their planned assessment in the method section. This observation may indicate that reports on harms outcomes in studies on the effectiveness of exercise therapy relatively often rely on spontaneous, self-reported AEs from participants without specific prompting. Although that reporting is in accordance with the guidelines on reporting of exercise therapy interventions such as the Consensus on Exercise Reporting Template (CERT) [52], in exercise therapy trials, the systematic assessment in all study arms is needed. Participants in the non-active study arms might also experience AEs related to non-therapeutic exercising or during the performance of daily activities. Moreover, study arms may vary in terms of participant interaction with trial personnel, which may also include varying intensities of supervision when different exercise therapy interventions are compared [52]. Furthermore, in case of a non-exercise control arm, both trial personnel and participants in the experimental arm(s) may be more inclined to attribute negative effects to the intervention. Thus, an imbalance in the opportunity to report AEs can introduce potential biases and limitations when comparing harm outcomes across different groups and potentially leading to an overestimation of harms in treatment groups.

The results of this review suggest that there is ample room to enhance the quality of harm assessment in studies on the effectiveness of supervised exercise therapy in RA or axSpA. In particular, there is a need for systematic approaches to capture harms outcomes including participant-reported AEs in all study arms [53]. Prespecifying harm outcomes is crucial as it helps researchers to systematically assess and capture any negative effects that may arise from the intervention [54]. Our inventory of the nature of harms could be used as a starting point for a consensual list of harms outcomes that should be prespecified in trials on the effectiveness of supervised exercise therapy in RA or axSpA. Prespecified harms outcomes could encompass, among others, episodes of increased disease activity, severe pain or fatigue, intensification of (pain) medication, and radiological progression in case of longstanding interventions. Structured questionnaires, and regular and consistent monitoring throughout the study duration in all study arms allow comprehensive evaluation of potential harms of exercising and provide a more balanced understanding of its potential risks and benefits. For that purpose, consensus on a set of recommended harms outcomes for exercises, both generic and for specific rheumatic conditions, is needed. By employing rigorous and standardized methods, researchers can minimize bias and ensure a more accurate evaluation of harm outcomes.

Due to the overall poor reporting of harms in the selected studies on exercise therapy interventions in inflammatory arthritis, the potential association between the patients' disease characteristics and the occurrence of harms could not be explored. To address this issue, studies that adequately report on the occurrence, nature, and severity of harms as well as potential risk factors are needed.

This review has some limitations we would like to address. First, we only included studies in English language, resulting in potential missed studies in other languages that could be relevant. Second, in our study, we focused on interventions in which the exercise sessions were all, or at least for a substantial part, supervised. Thereby, the results may not be generalizable to home-based exercise programs. Third, with the quality of reporting of harms in exercise trials in OA already being addressed, we focused on two types of inflammatory RMDs. Therefore, it remains to be established to what extent our findings are generalizable to other forms of RMDs such as fibromyalgia.

Finally, we presented only details of harms outcomes from studies describing data collection methods in the methods section(s) of the related paper(s). Although this allows an appropriate interpretation of the presented findings, this policy could have influenced the overview of the nature of harms outcomes we presented.

In summary, this systematic review found that the reporting on harms in RCTs on supervised exercise therapy in inflammatory arthritis is generally insufficient. Although the non-systematic assessment of harms outcomes, such as self-reported participant feedback in the intervention group(s) can offer valuable information in exercise therapy trials, it should be interpreted cautiously. Variations in study arm supervision and participant interaction may have an impact on reporting of harms, introducing potential biases. To improve the assessment of harm outcomes in studies on the effectiveness of exercise therapy, consensus on the most relevant harms outcomes in exercise therapy trials in RMDs, including prespecified thresholds where applicable, is recommended. Moreover, a better implementation of existing recommendations on the assessment and reporting of harms outcomes during the design, conduct, and reporting of studies is needed. This will help ensure more reliable and robust evaluations of the balance between harms and benefits of exercise therapy in future research.

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Author contributions

All authors have made substantial contributions to this project, spanning the conception, design, data acquisition, analysis, data interpretation, and/or the development of new software crucial to our work. MMHT, TPMVV, SFEW, JS, A-KRO, CBJ, KN, MGJG, and CHME made substantial contributions to the conception and design. MMHT, TPMVV, JWS and CHME made substantial contributions to the search strategy and selection of studies. MMHT, TPMVV and CHME have made significant contributions to the data extraction and analysis and interpretation of the data. Additionally, all authors were involved in drafting the manuscript and critically revising it to ensure the inclusion of important intellectual content. They have collectively approved the final version for publication. Moreover, the authors have agreed to be accountable for their respective roles in all aspects of the project, demonstrating their commitment to addressing any inquiries related to the accuracy or integrity of any part of the work with appropriate investigation and resolution. All authors take full responsibility for the integrity and accuracy of all aspects of their work.

Conflict of interest

The authors declare that they have no known conflicts of interest.

Supplementary files

- Supplementary file 1: Search strategy: adverse events in clinical trials on exercise therapy in patients with inflammatory arthritis or osteoarthritis.
- Supplementary file 2: Data extraction sheet for the reporting of harms outcomes in RCTs on supervised exercise in RA or axSpA.
- Supplementary file 3: Supplementary table 1: All included studies on RA and axSpA (N=65).

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Supplemental files

Supplementary file 1 Search strategy: adverse events in clinical trials on exercise therapy in patients with inflammatory arthritis or osteoarthritis.

PubMed

(((("Arthritis, Rheumatoid"[majr] OR "rheumatoid arthritis"[ti] OR "inflammatory arthritis"[ti] OR "Osteoarthritis"[majr] OR "osteoarthritis"[ti] OR "osteoarthrit*"[ti] OR "osteoarthrosis"[ti] OR "osteoarthro*"[ti] OR "degenerative arthritis"[ti] OR "degenerative arthriti*"[ti] OR "osteoarthrosis deformans"[ti] OR coxarthro*[ti] OR "gonarthro*"[ti] OR "Spondylarthropathies"[majr] OR "spondylarthropathies"[ti] OR "spondylarthropathy"[ti] OR "spondylarthropath*"[ti] OR "Marie-Strumpell Spondylitis"[ti] OR "Bechterew*"[ti] OR "Spondylitis, Ankylosing"[majr] OR "ankylosing spondylitis"[ti] OR "Spondyloarthritis Ankylopoietica"[ti] OR "Ankylosing Spondylarthritis"[ti] OR "Spondylarthritis Ankylopoietica"[ti] OR "Bechterew*"[ti] OR "Marie-Struempell Disease"[ti] OR "Marie Struempell Disease"[ti] OR "Rheumatoid Spondylitis"[ti] OR "Spondylitis Ankylopoietica"[ti] OR "Ankylosing Spondyloarthritis"[ti] OR "Spondylarthritis"[majr] OR "spondyloarthrit*"[ti] OR "spondyloartrit*"[ti] OR 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Embase (OVID)

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Web of Science

((TI=("Rheumatoid Arthritis" OR "rheumatoid arthritis" OR "inflammatory arthritis" OR "Osteoarthritis" OR "osteoarthritis" OR osteoarthrit* OR "osteoarthrosis" OR osteoarthro* OR "degenerative arthritis" OR degenerative arthriti* OR "osteoarthrosis deformans" OR "coxarthro*" OR gonarthro* OR "Spondylarthropathy" OR "spondylarthropathies" OR "spondylarthropathy" OR spondylarthropath* OR "Marie-Strumpell Spondylitis" OR Bechterew* OR "Ankylosing Spondylitis" OR "ankylosing spondylitis" OR "Spondyloarthritis Ankylopoietica" OR "Ankylosing Spondylarthritis" OR "Spondylarthritis Ankylopoietica" OR "Bechterew*" OR "Marie-Struempell Disease" OR "Marie Struempell Disease" OR "Rheumatoid Spondylitis" OR "Spondylitis Ankylopoietica" OR "Ankylosing Spondyloarthritis" OR "Spondylarthritis" OR "spondyloarthrit*" OR "spondyloartrit*" OR "spondylo-arthrit*" OR "Reactive Arthritis" OR "Reactive Arthritis" OR "Post-Infectious Arthritis" OR "Postinfectious Arthritis" OR "Reiter Syndrome" OR "Reiter's Disease" OR "Reiters Disease" OR "Reiter Disease" OR "Psoriatic Arthritis" OR "Arthritic Psoriasis" OR "Psoriatic Arthritis" OR "Psoriasis Arthropathica" OR "Psoriatic Arthropathy" OR "Psoriatic Arthropathies") AND TI=("Exercise Therapy" OR "exercise therapy" OR "exercise therap*" OR "Muscle Stretching Exercises" OR "Muscle Stretching Exercise" OR "Static Stretching" OR "Passive Stretching" OR "Static-Passive Stretching" OR "Static Passive Stretching" OR "Isometric Stretching" OR "Active Stretching" OR "Static-Active Stretching" OR "Static Active Stretching" OR "Ballistic Stretching" OR "Dynamic Stretching" OR "PNF Stretching" OR "Plyometric Exercise" OR "Plyometric Exercises" OR Plyometric Drill* OR "Plyometric Drills" OR "Plyometric Training" OR "Plyometric Trainings" OR "Stretch-Shortening Exercise" OR "Stretch Shortening Exercise" OR "Stretch-Shortening Exercises" OR "Stretch-Shortening" OR "Stretch Shortening" OR "Stretch-Shortening Drills" OR "Stretch-Shortening Cycle Exercise" OR "Stretch Shortening Cycle Exercise" OR "Stretch-Shortening Cycle Exercises" OR "Resistance Training" OR "Strength Training" OR "training" OR "Weight-Lifting" OR "Weight Lifting" OR "Weight-Bearing" OR "Weight Bearing" OR "Exercise" OR exercis* OR "stretching" OR "Exercise" OR "Exercises" OR "Physical Exercise" OR "Physical Exercises" OR "Isometric Exercises" OR "Isometric Exercise" OR "Aerobic Exercises" OR "Aerobic Exercise" OR "Circuit-Based Exercise" OR "Cool-Down Exercise" OR "Cool-Down Exercises" OR "Physical Conditioning" OR "Running" OR "Jogging" OR "Swimming" OR "Walking" OR "Warm-Up Exercise" OR "Warm-Up Exercises" OR "Physical Exertion" OR "Physical Effort" OR "Physical Efforts" OR "Fitness" OR "Physical Fitness" OR "Fitness" OR "Endurance" OR "Physical Endurance" OR "Anaerobic Threshold" OR "Exercise Tolerance" OR "Exercise Movement" OR "Bicycling" OR "Walking" OR "Motor Activity" OR "Physical Activity" OR "Physical Activity" OR exertion* OR "Sport" OR "sports" OR "sport" OR "Athletic Performance" OR "Cardiorespiratory Fitness" OR "Physical Endurance" OR "Physical Fitness" OR "Bicycling" OR "Golf" OR "Gymnastics" OR "Mountaineering" OR "Racquet Sports" OR "Tennis" OR "Running" OR "Jogging" OR "Skating" OR "Snow Sports" OR "Skiing" OR "Swimming" OR "Track and Field" OR "Volleyball" OR "Walking" OR "Weight Lifting" OR treadmill* OR row OR rows OR rowing OR muscle strength* OR "Range of Motion" OR "Joint Range of Motion" OR "Joint Flexibility" OR "Range of Motion" OR "Postural Balance" OR "Postural Balance") AND TS=("effectiveness" OR effectiv* OR "effect" OR "effects" OR "Safety" OR "safety" OR "safe" OR "unsafe" OR "Risk" OR "risk" OR "risks" OR "feasibility" OR feasibil* OR "Feasibility Study" OR "efficacy" OR improve* OR (adverse* NOT "no adverse")) AND TS=("meta analysis" OR "systematic review" OR "Randomized Controlled Trial" OR "randomized controlled trial (topic)" OR "Randomization" OR "RCT" OR random*))

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Emcare (OVID)

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PsycINFO (EbscoHOST)

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Academic Search Premier (IEbscoHOST)

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PEDro

Title or abstract: arth* OR spondylitis
Intervention: fitness training
Subdiscipline: Musculoskeletal

Supplementary file 2 Data extraction sheet for the reporting of harms outcomes in RCTs on supervised exercise in RA or axSpA.

Study characteristics	**Author and year of Publication**	**…….. et al. (XXXX)**
	Diagnosis RA/axSpA	RA☐axSpA☐
	Number of patients per treatment arm and the description of treatment arms Description of intervention per treatment arm	Treatment arm 1: ☐ N=(…); Description arm 1: Treatment arm 2: ☐ N=(…); Description arm 2: Treamtent arm 3: ☐ N=(…); Description arm 3: Treatment arm 4: ☐ N=(…); Description arm 4: Treatment arm 5: ☐ N=(…); Description arm 5: Treatment arm 6: ☐ N=(…); Description arm 6:
Reporting of harms	**Any harms described in the manuscript?**	Yes☐No☐
	Any harms described in the Title or Abstract sections?	Yes☐No☐
	Any harms described in the Introduction section?	Yes☐No☐
	A. Specific objectives or hypotheses for outcomes of harms?	Yes☐No☐
	Any harms described in the Methods section?	Yes☐No☐
	<u>Prespecified harms outcomes</u> Method and timing of assessment described?	Yes☐No☐
	<u>Non-prespecified harms outcomes</u> Method and timing of systematic assessment (active surveillance) described?	Yes☐No☐
	<u>Non-prespecified harms outcomes</u> Method of passive surveillance of harms outcomes described?	Yes☐No☐
	Any harms described in the Results section? (including Figures or Tables)	Yes☐No☐
	B. <u>Prespecified harms outcomes</u> Reported details on prespecified harms outcomes?	Yes☐No☐
	C. <u>Non-prespecified harms outcomes</u> Reported details (timing, duration or severity) on non-prespecified harms outcomes?	Yes☐No☐
	D. <u>Non-prespecified harms outcomes</u> Reported zero events if no harms were observed?	Yes☐No☐ Not applicable☐

Supplementary file 2 (continued) Data extraction sheet for the reporting of harms outcomes in RCTs on supervised exercise in RA or axSpA.

	Any harms described in the Discussion section?	**Yes☐No☐**
	E. Reflection on findings on harms of the study?	Yes☐No☐
Description of methods of collection in the Methods section	If Method and timing of assessment was described for prespecified harms outcomes, what was described in the paper?	Exact description in methods section:
	If Method and timing of systematic assessment (active surveillance) was described for non-prespecified harms outcomes , what was described in the paper?	Exact description in methods section:
	If Method of passive surveillance of harms outcomes was described for non-prespecified harms outcomes, what was described in the paper?	Exact description in methods section:
Description of nature of harms in the Results or Discussion sections (only in case reporting of the method of ascertainment in the Method section)	If Method and timing of assessment was described for prespecified harms outcomes, what was the nature of the reported harms described in the Results section?	Harms outcomes Yes☐No☐ nature:
	If Method and timing of active surveillance or passive surveillance was described for non-prespecified harms outcomes, what was the nature of the reported harms described in the Results section per treatment arm?	SAE(s) per treatment arm: Yes☐No☐ nature: AE(s) per treatment arm: Yes☐No☐ nature:

Abbreviations: RA, rheumatoid arthritis; axSpA, axial spondyloarthritis; SAE, Serious adverse event; AE, adverse event.

Supplementary table 1 All included studies on RA and axSpA (N=65).

Author & publication year	Description of intervention arms	Duration and frequency of intervention	Harms anywhere in the manuscript
RA (N=40)			
Loeppenthin et al. 2022 [1]	n=17; Aerobic exercise intervention n=21; Usual care	3 sessions per week for 6 weeks	Yes
Gautam et al. 2021 [2, 3]	n=70; Yoga-based lifestyle intervention n=70; Usual care	5 sessions per week for 8 weeks	No
McKenna et al.2021 [4]	n=12; Walking-based exercise n=12; Advice on the benefits of exercise	28 sessions (2-5 per week) for 8 weeks	Yes
Pukšić et al. 2021 [5]	n=30; Yoga intervention n=30; Education control	2 sessions per week for 12 weeks	Yes
Cerşit et al. 2020 [6]	n=36; Cardiac rehabilitation program + Home exercise program n=33; Home exercise program	3 sessions per week for 10 weeks, 3 sessions per week home exercise program for weeks 11-24	No
Ganesan et al. 2020 [7]	n=83; Yoga group n=83; Usual care	3 sessions per week for 12 weeks	No
García-Morales et al. 2020 [8-10]	n=36; Mediterranean diet + Dynamic exercise program n=37; Dynamic exercise program n=40; Mediterranean diet n=31; Usual care	2 sessions per week for 24 weeks	Yes
Rezaei et al. 2020 [11]	n=28; Aerobic walking program n=28; Usual care	30 sessions (3-5 per week) for 8 weeks	No
Gautam et al. 2019 [12]	n=36; Yoga based mind body based intervention n=36; Usual care	5 sessions per week for 8 weeks	No
Lange et al. 2019 [13-16]	n=36; Aerobic and resistance exercise + home based-exercise n=36; Home-Based exercise	20 weeks program, consisting of 3 sessions per week exercise and 2-5 sessions per week home-based exercise.	Yes
Ward et al. 2018 [17]	n=13; Group and home-based yoga n=13; Usual care	8 weeks consisting of 1 group session per week, 3 sessions per week home-based yoga.	Yes
Lourenzi et al. 2017 [18]	n=33; Progressive resistance strength program n=33; Usual care	2 sessions per week for 12 weeks	No
Siqueira et al. 2017 [19]	n=33; Water-based exercise n=33; Land-based exercise n=34; No exercise	3 sessions per week for 16 weeks	Yes
Shapoorabadi et al. 2016 [20]	n=18; Aerobic cycling program n=18; Usual care	3 sessions per week for 8 weeks	Yes
Lamb et al. 2015 [21-24]	n=246; Hand exercise program n=244; Usual care	6 sessions in total for a 12 weeks period + daily home-based exercise	Yes
Seneca et al. 2015 [25]	n=25; Partly supervised exercise program n=26; Self-administered exercise program	2 sessions per week for 6 weeks, recommended to keep exercising for weeks 6-12	Yes
Jahanbin et al. 2014 [26]	n=32; Exercise training intervention n=32; Usual care	2 session per week for 8 weeks	Yes
Cima et al. 2013 [27]	n=13; Hand Exercise program n=7; Usual care	20 sessions (2 per week) for 2 months and home exercises (not specified how often)	Yes
da Silva et al. 2013 [28]	n=51; Sensorimotor exercise group n=51; Usual care	2 sessions per week for 16 weeks	No
Janse van Rensburg et al. 2012 [29]	n=19; Exercise group n=18; Sedentary group	2-3 sessions per week for 12 weeks	No
Strasser et al. 2011 [30]	n=20; Strength & endurance training n=20; Stretching exercises	2 sessions per week for 26 weeks	Yes
Flint-Wagner et al. 2009 [31]	n=16; Supervised strength training n=8; Usual care	3 sessions per week for 16 weeks	Yes
Hsieh et al. 2009 [32]	n=15; Supervised aerobic exercise n=15; Home-exercise	3 sessions per week for 8 weeks	Yes
Lemmey et al. 2009 [33, 34]	n=18; Progressive resistance training n=18; Range of movement training	2 sessions per week for 24 weeks	Yes
Bastiana et al. 2008 [35]	n=8; Muscle strengthening exercises and heat therapy + range of motion home exercises n=9; Heat therapy	6 weeks, consisting of 3 sessions per week exercises + heat therapy, daily home exercises	Yes
Wang et al. 2008 [36]	n=10; Tai Chi exercises n=10; Stretching & wellness education	2 sessions per week for 12 weeks	Yes
Eversden et al. 2007 [37]	n=58; Hydrotherapy n=57; Land-based exercises	1 session per week for 6 weeks	No
Bilberg et al. 2005 [38]	n=20; Exercise in a temperate pool n=23; Usual care	2 sessions per week for 12 weeks	No

Supplementary table 1 (continued) All included studies on RA and axSpA (N=65).

Author & publication year	Description of intervention arms	Duration and frequency of intervention	Harms anywhere in the manuscript
McMeeken et al. 1999 [46]	n=17; Knee extensor and flexor muscle training n=18; Usual care	14 sessions in 6 weeks period	Yes
Hall et al. 1996 [47]	n=35; Hydrotherapy n=35; Seated immersion n=34; Land exercise n=35; Progressive relaxation	2 sessions per week for 4 weeks	Yes
van den Ende et al. 1996 [48]	n=25; Intensive dynamic group exercises n=25; range of motion and isometric exercise group n=25; range of motion and isometric exercise individually n=25; range of motion and isometric exercise at home	3 sessions per week for 12 weeks	Yes
Ekdahl et al. 1994 [49, 50]	n=15; High intensity dynamic exercise program n=15; Usual care	2 session per week for 6 weeks + home training for 6 months (frequency not clear)	Yes
Lyngberg et al. 1994 [51]	n=12; Progressive interval training n=12; No training	2 sessions per week for 3 months	Yes
Baslund et al. 1993 [52]	n=9; Physical training program n=9; no training	4-5 sessions per week for 8 weeks	Yes
Hansen et al. 1993 [53]	n=14; Self-training n=14; Training in physiotherapy practice n=14; Group training n=13; Group training + Pool n=13; No training	1 session per week + daily home exercise for 24 months	Yes
Ekdahl et al. 1990 [54]	Only total provided n=67 Dynamic exercise program: 12 scheduled visits Dynamic exercise program: 4 scheduled visits Static exercise program: 12 scheduled visits Static exercise program: 4 scheduled visits	2 session per week for 6 weeks + home exercise for 3 months (frequency not clear)	Yes
Minor et al. 1989 [55]	n=19; Aerobic exercise n=9; Nonaerobic exercise (Range of motion (ROM) exercise)	3 sessions per week for 12 weeks	Yes
van Deusen et al. 1987 [56]	n=23; Range of motion dance program n=23; Usual care	8 weeks including, 1 session per week group session, daily home exercise	No
AxSpA (N=25)			
Acar et al.2023 [57]	n=30; Pilates training group n=30; Home-based exercise group	3 sessions per week for 8 weeks	No
Oksüz et al. 2023 [58]	n=14; Clinical Pilates exercise + aerobic exercise n=14; Aerobic exercise	3 sessions per week for 8 weeks	No
Yentür et al. 2022 [59]	n=20; Pilates training group n=20; Home-based stretching exercises	3 sessions per week for 8 weeks	No
Gandomi et al. 2022 [60]	n=17; Aqua Pilates n=17; Aqua stretching n=17; Usual care	4 sessions per week for 6 weeks	No
Calik et al. 2021 [61]	n=22; Aerobic exercise + spinal mobility exercises n=22; Spinal mobility exercises	3 sessions per week for 12 weeks	Yes
Gurpinar et al. 2021 [62]	n=16; Aquatic exercise group n=13; land-based exercise group n=17; Home exercise group	2 sessions per week for 12 weeks	Yes
Cetin et al. 2020 [63]	n=18; Tai Chi group n=18; Home-based exercises group	2 sessions per week for 10 weeks	Yes
Ma et al. 2020 [64]	n=42; Tai Chi + exercise therapy n=42; Exercise therapy	2 sessions per week for 12 weeks	No
Sveaas et al. 2019 [65-68]	n=50; High-intensity aerobic & strength exercises n=50; Usual care	3 sessions per week for 12 weeks	Yes
Xie et al. 2019 [69]	n=30; Baduanjin qigong training n=30; No training	2-3 sessions per week for 12 weeks	Yes
de Souza et al. 2017 [70]	n=30; Resistance exercises on a Swiss ball n=30; Usual care	2 sessions per week for 16 weeks	Yes

Supplementary table 1 (continued) All included studies on RA and axSpA (N=65).

Author & publication year	Description of intervention arms	Duration and frequency of intervention	Harms anywhere in the manuscript
Drăgoi et al. 2016 [71]	n=27; inspiratory muscle training + exercise training n=27; Exercise training	8 weeks consisting of 1 session per week of exercise, 3 sessions per week of inspiratory muscle training	Yes
Fang et al. 2016 [72]	n=24; Supervised exercise & home-based exercise n=20; Home-based exercise	3 sessions per week for 6 months + home-based exercises (frequency not clear)	Yes
Karahan et al. 2016 [73]	n=28; Exergame program n=29; No exercise	5 sessions per week for 8 weeks	Yes
Jennings et al. 2015 [74]	n=35; Aerobic exercise (walking) + stretching exercises n=35; Stretching exercises	3 sessions per week for 12 weeks	No
Taşpinar et al. 2015 [75, 76]	n=20; Hospital based calisthenic exercise n=20; Home-based calisthenic exercise	5 sessions per week for 8 weeks	No
Dundar et al. 2014 [77]	n=35; Aquatic exercise n=34; land-based exercise	5 sessions per week for 4 weeks	Yes
Sveaas et al. 2014 [78, 79]	n=13; Endurance and strength training n=15; Usual care	3 sessions per week for 12 weeks	Yes
Niedermann et al. 2013 [80]	n=53; Cardiovascular training n=53; Attention control	2 sessions per week for 12 weeks	Yes
Altan et al. 2012 [81]	n=30; Pilates exercise program n=25; Usual care	3 sessions per week for 12 weeks	Yes
Cagliyan et al. 2007 [82]	Only total provided n=46 Supervised exercise Home-based exercise	2 hours per week for 6 months	No
Ince et al. 2006 [83]	n=15; Exercise intervention n=15; Usual care	3 sessions per week for 3 months	No
Analay et al. 2003 [84]	n=27; Group exercise therapy as hospital outpatients n=24; Exercise program at home	3 sessions per week for 6 weeks	No
Helliwell et al. 1996 [85]	n=15; In-patient intensive physiotherapy n=15; Hydrotherapy and exercises n=14; Home exercises	3 sessions per week for 3 weeks	No
Hidding et al. 1993 [86-88]	n=15; Group exercise + Home-based exercise n=15; Home-based exercise	9 months consisting 1 session per week group exercise, home-based exercise (unclear how often)	No

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9

Chapter 9

Summary & general discussion

Summary

Rheumatoid arthritis (RA) is a form of inflammatory arthritis, resulting in functional disability in a significant proportion of patients. To prevent or reduce functional limitations in people with RA, exercise therapy is a common treatment option that is advocated in professional guidelines. These recommendations are based on sufficient evidence for the effectiveness of exercise therapy in RA. However, most studies were executed in people with RA and a relatively favorable health status. Evidence for its (cost-)effectiveness has not been established for people with RA and severe functional disability. Severe functional disability may result from e.g., persistent high disease activity, joint damage, complications of the disease or its treatment or comorbidity. In addition to the scarcity of knowledge on the (cost-)effectiveness of exercise therapy in this specific subgroup, there are also knowledge gaps with respect to the optimal outcome measures for the evaluation of functional ability and the monitoring of safety of exercises in exercise therapy trials. To address these knowledge gaps, the first part of this thesis focuses on the evaluation of the effectiveness and cost-effectiveness of a longstanding, personalized, supervised, active exercise therapy intervention compared to usual care in patients with RA with severe functional disability (Chapters 2-4). In the second part, the usage and applicability of various outcome measures concerning the effectiveness and safety of exercise therapy in RA are explored (Chapters 5-8).

Chapter 1 describes the epidemiology and pathophysiology of RA and its impact according to the various dimensions of the International Classification of Functioning, Disability and Health (ICF). The pharmacological and non-pharmacological management of RA in the Netherlands are discussed, with an emphasis on rehabilitative treatment and the role of exercise therapy. In addition, outcome measures to evaluate functional ability in RA are reviewed, as well as the measurement of harms outcomes in exercise therapy trials in RA.

Chapter 2 describes the protocols of two parallel randomized clinical trials (RCTs) on exercise therapy in patients with RA or axial spondyloarthritis (axSpA), of which the L-EXTRA (Longstanding EXercise Therapy in patients with Rheumatoid Arthritis) study is the primary focus of this thesis. The protocol of the L-EXTRA study concerns a single-blinded, randomized clinical trial (RCT) on the (cost-)effectiveness of longstanding, personalized, active exercise therapy versus usual care in people with RA and severe functional disability. The study aimed to include a total of 215 participants. The

intervention, delivered by trained primary care physical therapists, comprised individualized goal setting, active exercises, education, and self-management support regarding physical activity. The primary endpoint for effectiveness was the change in the Patient-Specific Complaints activity ranked 1 (PSC1) at 52 weeks. Secondary endpoints encompassed PSC activities ranked 2 and 3, the Health Assessment Questionnaire-Disability Index (HAQ-DI), the Patient-Reported Outcomes Measurement Information System Physical Function 10-item (PROMIS PF-10), the Rheumatoid Arthritis Quality of Life questionnaire (RAQoL), the 6-minute walk test (6MWT), and the Short Form-36 Physical and Mental Component Summary Scales (SF-36 PCS and MCS). With respect to harms, serious adverse events (SAEs) or adverse events (AEs) that were (potentially) linked to the intervention were prospectively recorded in the intervention group by the treating physical therapists. For the cost-effectiveness analysis the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) and the EuroQol-Visual Analogue Scale (EQ-VAS) were used to determine utilities and quality adjusted life years (QALYs). Moreover, regarding the costs, questionnaires on health care usage and work were administered at baseline, and at 12, 26 and 52 weeks.

Chapter 3 presents the results on the effectiveness at 52 weeks. Between March 2020 and December 2021, a total of 217 eligible participants were included. After the randomization two participants withdrew immediately (one from each group) and these individuals were substituted to achieve the intended total of 215 participants (109 intervention group, 106 usual care group). Eleven participants (4 intervention group (4%), 7 usual care group (7%)) were lost to follow-up between baseline and 52 weeks. In the intervention group, 104 participants (95%) started the intervention, using on average 39 sessions (SD 15.9). Moreover, 70 (66%) participants in the usual care group received physical therapy outside the study intervention over the 52-week study period. At 52 weeks, the improvement in the PSC1 was significantly larger in the intervention group (mean difference [95% confidence interval (CI)]-1.7 [-2.4, -1.0]). 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] meter), except for the SF-36 MSC (+2.54 [-0.47, 5.54]). Only one mild, transient AE occurred in the intervention group.

In conclusion, after 1 year, longstanding, supervised exercise therapy proved more effective than usual care in individuals with RA and severe functional limitations with respect to patient-reported and performance-based functional ability and physical quality of life.

Chapter 4 describes the economic analysis of the study presented in Chapters 2 and 3. The cost-utility analysis was conducted from the societal perspective and with a one-year follow-up. Costs and QALY differences were analyzed according to the intention-to-treat principle using cost-effectiveness acceptability curves. The mean direct costs of the intervention were €1423 per participant in the intervention group. The 1-year total medical costs differed by €754 (95% CI €-3012 to €4519) between the intervention and usual care groups, with a non-statistical significance in favor of the usual care group. The 1-year total societal cost were also non-significantly in favor of the usual care group with a small difference of €180 (95% confidence interval (CI) €-4493 to €4852). The QALYs were non-significantly in favor of the intervention group by 0.02 according to the EQ-5D-5L (95% CI −0.05 to 0.09) and by 0.04 according to the EQ-VAS (95% CI 0.00 to 0.08). For a willingness-to-pay threshold of €50,000 per QALY, the intervention was the cost-effective strategy with 60% certainty. In conclusion, despite the somewhat higher costs in the intervention group, but given its better clinical outcomes as compared to usual care, the results of this study suggest that there are no economic reasons to refrain from longstanding exercise therapy in people with RA and severe functional limitations.

Patient-specific outcome measures provide insight into the nature and severity of specific limitations as indicated by the individual patient. Such instruments may not only support personalized goal setting in rehabilitative interventions, including exercise therapy, but can also be used as outcome measures in clinical trials. The abovementioned PSC is an example of such a patient-specific measure and was found to have the ability to detect changes in a patient's perception of functioning and/or participation over time in previous research. It is administered through a face-to-face interview and identifies the three limited activities that are most relevant for them, with the level of difficulty for each of these activities scored from 0 = easy, to 10 = impossible to do.

Using the information from the PSC that was administered in the clinical trial described in Chapters 2-4, the study in **Chapter 5** aimed to describe the functional limitations of individuals with RA or axSpA. Baseline data from 206 RA and 155 axSpA participants in the RCT described in Chapters 2, 3 and 4 and the parallel trial in axSpA, were analyzed. The three most limited activities obtained from the PSC were linked to the ICF using standardized methodology. The frequencies of observed ICF categories were calculated and compared with Activities and Participation items of the ICF Core Sets for RA (32 second-level categories) and Ankylosing Spondylitis (AS) (24 second-level categories). ICF Core Sets include those ICF categories that are considered most relevant for people with a specific condition and comprise both a Comprehensive and a Brief version. The results of the study showed both for RA and axSpA, most limitations listed in the PSC were, related to the ICF chapter "Mobility", and included activities such as "Walking", "Changing basic body position", "Stair climbing", "Grasping", "Lifting", and "Maintaining a standing position". A significant proportion of identified second-level categories matched those in the ICF Core Sets for RA and AS. Thirteen ICF categories (four in RA and nine in axSpA) were found outside the categories included in Comprehensive Core Sets for RA or AS. These categories comprised "Stair climbing" in RA and "Fine hand use" in axSpA, of which the prevalence exceeded 5% in our study populations. Overall, the findings showed a relatively high prevalence of mobility-related limitations in individuals with RA or axSpA and severe functional disability. Moreover, it was seen that limitations were to a large extent, but not fully, aligned with the contents of the corresponding ICF Core Sets.

Whereas the analysis of the content of a patient-specific instrument such as the PSC yields relevant information on the nature and severity of functional limitations in people with RA and functional disability, such instruments are not commonly administered in exercise trials. Although patient-specific instruments enable the comparison of severity within patients over time and across patients and patient populations, the nature of the functional limitations cannot be directly compared across patients or patient populations. For such purposes, measurement of functional disability by means of a standardized questionnaire is more suitable and far more common, with the HAQ-DI being the most often used outcome measure in RA. The HAQ-DI is a self-administered questionnaire assessing the difficulty with performing 20 activities across eight domains (Dressing, Arising, Eating, Walking, Personal hygiene, Reaching, Gripping, Usual activities). Item scores range from 0-3 (0 no difficulty to 3 is unable to do), whereas the use of help from another person or

assistive device can be accounted for in the score. The domain scores range from 0 to 3, and the total score can range from 0–1 (mild), to >1–2 (moderate-severe), and >2–3 (severe-very severe). The results of the HAQ-DI are usually reported as the total score. However, an analysis of the eight dimensions and/or 20 individual items could, like the abovementioned PSC, yield relevant information on the nature and severity of functional disability in RA.

Chapter 6 aimed to explore the nature and extent of functional limitations in individuals with RA and severe disabilities according to the HAQ-DI, including the associations with patient and disease characteristics and outcome measures. Baseline data from 215 participants in the L-EXTRA study described in Chapters 2, 3 and 4 were analyzed. To determine the associations between the HAQ-DI score on the one side and patient characteristics and other outcome measures on the other side, these measures were compared between patients with a HAQ-DI score <2 and ≥2, using the Student's t-test or Chi-squared test. The mean HAQ-DI score of the 215 participants was 1.7 (SD 0.5). A total of 120 participants (56%) had a HAQ-DI domain score ≥1 in all domains, with 170 (79%) having a score ≥1 in 7 or all 8 HAQ-DI domains. Severe limitations were most frequent in the domains “Usual Activities”, “Gripping”, “Reaching” and “Personal hygiene”, with 75% or more of the study population having a domain score of ≥2. Patients with higher HAQ-DI scores were significantly older, had a longer disease duration, were not being employed, and had one or more joint replacements than those with lower HAQ-DI scores. Additionally, they had worse baseline scores for other measures of functioning and physical quality of life. From this study it was concluded that the large majority of patients with RA and severe functional disability had limitations in most of the HAQ-DI domains. The HAQ-DI score was associated with various sociodemographic characteristics and measures of physical functioning. Additional research is needed to validate and substantiate these associations in other populations including patients with different levels of severity of functional disability.

A relatively recent and generic measure of physical functioning is the PROMIS PF-10, an instrument that was used in the RCT described in Chapters 2, 3 and 4. It is one of the multiple PROMIS instruments. PROMIS® comprises a set of person-centered measures that are developed to evaluate and monitor physical, mental, and social health in adults and children. PROMIS measures can be used within the general population and within individuals living with chronic conditions. These measures yield standardized scores, expressed as T-scores centered around the general population. PROMIS measures were found to have greater precision than most conventional measures, thereby increasing the efficiency of clinical trials. Although PROMIS measures are likely to be of value in research in people with inflammatory arthritis, little is known on their actual usage in clinical studies.

In **Chapter 7** a systematic literature review exploring the use and outcomes of PROMIS measures in clinical studies involving individuals with RA or axSpA is described. For that purpose, a literature search across nine electronic databases was conducted, focusing on articles published from the year 2007, when PROMIS was introduced, onward. Original clinical studies in patients with RA and/or axSpA that were reporting the use of one or more PROMIS measures were included. The selection of studies and data extraction was done by two researchers. A total of 29 studies (25 for RA, 3 for axSpA, and 1 for both) met the inclusion criteria. Two general PROMIS measures (PROMIS Global Health, PROMIS-29) and 13 domain-specific PROMIS measures were reported, with the PROMIS Pain Interference, Physical Function (including the PROMIS PF-10), Fatigue, and Depression measures being the most frequently used. Results indicated that the health status of participants was generally worse than the general population mean. Also, there was significant variability in the selection of PROMIS measures and their various versions, highlighting the need for more standardization to facilitate meaningful comparisons across studies.

Clinical decisions on any intervention in health care are usually based on the appropriate balance between the expected desired health benefits and undesired harms or side effects. Regarding the knowledge on the possible harms of exercises in inflammatory arthritis, the knowledge is relatively scarce. In **Chapter 8**, a systematic literature review evaluating the reporting quality and nature of harms in clinical studies investigating the effectiveness of supervised exercises in patients with RA or axSpA is presented. The review included RCTs in adults with RA or axSpA comparing exercise therapy (aerobic, muscle strengthening,

range of motion, neuromotor, stretching, or mind–body exercises) with at least six supervised sessions with a control condition. A search strategy with key terms related to RA and axSpA, exercise therapy and harms was applied in eight databases, until February 2023. Study selection and data extraction was independently performed by two of three reviewers. In total 40 RA and 25 axSpA RCTs were included, of which 29 (73%) and 13 (52%), reported any information on harms. Only 13 (33%) of RA and 4 (16%) of axSpA RCTs provided details on the collection of harm outcomes in the methods section. Prespecified harms outcomes were reported in 8 (20%) RA and 2 (8%) axSpA RCTs, while non-specified harms outcomes were reported by 6 (15%) RA and 4 (16%) axSpA RCTs. Prespecified harms included measures of pain, disease activity, inflammation, and structural joint changes. Non-prespecified harms outcomes varied widely, with pain being the reported most. Given the observed overall poor reporting quality, and the variability regarding the nature of outcomes that were considered as harms, there is likely a need for improved reporting of harms outcomes in trials on exercise therapy in patients with RA or axSpA. In that respect, the use of the Consolidated Standards of Reporting Trials (CONSORT) Harms 2022 Checklist for comprehensive trial design, conduct, and reporting is recommended.

General discussion

Aim 1: Investigate the (cost-)effectiveness of longstanding supervised exercise therapy in people with RA and severe functional disability.

Effectiveness of longstanding supervised exercise therapy

The randomized clinical trial (RCT) described in Chapters 2 and 3 of thesis established the effectiveness of longstanding supervised exercise therapy for individuals with RA and severe functional disability. At 52 weeks, the intervention group showed significantly greater improvements than the usual care group for various measures of functional ability and quality of life, except for the SF-36 Mental Component Summary Scale (MCS).

Despite efforts to disseminate information on the trial, reaching potentially eligible participants proved difficult, especially as the trial ran from 2020-2022, during the COVID-19 pandemic. In centers where recruitment was intensified, enrollment rates increased, even more so when patients were invited via personalized mailings. This observation suggests that dissemination of information on the study may have been incomplete or insufficient. Also, other factors may have played a role, such as the clinicians' potential lack of awareness of functional limitations in people with RA they were treating or time constraints during consultations. This assumption was formulated based on the observation that the majority of individuals with RA enrolled themselves in the study, while the minority was referred by healthcare professionals. Nevertheless, due to great efforts of many stakeholders in the project including clinicians, the recruitment was eventually completed with minimal delay.

The characteristics of the included participants corresponded to those with the intended target group of people with RA and severe functional disability. The severity and complexity of the health status of the included participants was illustrated by their relatively high mean HAQ-DI score of 1.7 (SD 0.5), and the substantial proportion of participants with one or more comorbidities (96%) and/or meeting the criteria for Difficult-to-treat RA (47%) [1, 2].

To our knowledge, this clinical trial is the first to evaluate a personalized, active, longstanding exercise therapy intervention in a specific population of individuals with RA and severe functional disability. In general, the findings align with those of previous literature on the effectiveness of exercise therapy in RA [3-8]. These studies only included participants with a favorable health status, except for one RCT that was conducted in a rehabilitation setting [9]. That study specifically included RA patients with active disease [9] who had a mean baseline HAQ-DI score similar to the mean score in the current study. Despite a small sample and short duration of the intervention (on average 30 days), that study found a clinically relevant but non-significant improvement of −0.2 (95% CI −0.7, 0.3) of the HAQ-DI. The results are consistent with those of our study, indicating the potential of exercise therapy for those individuals with RA patients with complex health problems usually excluded from exercise trials.

In our study, we used the PSC [10-12], a patient-specific measurement instrument to evaluate functional disability, which is not commonly applied in exercise therapy trials. One RCT on a longstanding, intensive exercise therapy intervention in RA used another patient-specific instrument; the McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR) [13]. Both PSC and MACTAR were able to demonstrate the benefit of an exercise intervention compared to usual care. With respect to the ability of the HAQ-DI to detect an effect of exercise therapy, in the study on the longstanding high intensity intervention only a small effect was seen according to the HAQ-DI, and only at the 2-year endpoint [13]. The lack of a clinically relevant effect on the HAQ-DI in that study is likely due to the much better baseline scores, indicating less functional disability in that study population [13].

The present study demonstrated, in addition to a positive effect on various patient-reported outcome measures (PROMs), also a notable effect on the 6MWT. This is partly in line with other RCTs using both PROMs and performance-based outcomes to evaluate functional disability of an exercise intervention as compared to a control condition, yet in people with RA without serious comorbidity [14, 15]. Those studies demonstrated significant differences between groups for the performance-based measures but not for the PROMs [14, 15].

Previous studies in RA have demonstrated an effect of exercise therapy on mental well-being [13, 16, 17]. In our study, no effect of the intervention was seen for mental functioning as measured by SF-36 MCS. In this respect it is worth noting that the average baseline SF-36 MCS score in our trial was relatively favorable. This may have limited the room for improvement of mental health on the group level in this trial, whereas the sample size did not allow a subgroup analysis of those patients with the worst SF-36 MSC scores.

Regarding the intervention itself, the framework of the WHO International Classification of Functioning, Disability and Health (ICF) [18] and the Hypothesis Oriented Algorithm for Clinicians (HOAC)-II [19, 20] was followed. Thereby, the intervention had similarities with the interventions employed in two other RCTs, one in the elderly with mobility problems (Coach2Move) [21, 22] and one in individuals with knee osteoarthritis and complex health problems [23]. The interventions in these studies were used for the development of the intervention employed in the L-EXTRA study (Longstanding Exercise Therapy in patients with Rheumatoid Arthritis. As a result, in our study, the intervention protocol comprised 1) a comprehensive assessment (biopsychosocial assessment based on national physical therapy guidelines, with special focus on complex RA and multimorbidity during history-taking and examination following); 2) setting of treatment goals; 3) a collaboratively developed goal-based treatment plan, incorporating active exercises (aerobic, muscle strengthening, flexibility, neuromotor exercises) and education/self-management support, in particular regarding promotion of physical activity; 4) support and regular monitoring/evaluation of treatment goals and, if needed adjustment of the intervention (treatment modalities, dosage). The favorable findings of the present and these two previous studies [21-23] suggest the potential of exercise therapy in subgroups of patients who are often excluded from clinical trials, provided that treatment comprises the abovementioned structured approach. As such, the potential is dependent on adherence to a standardized treatment protocol during its implementation. Overall, it seems justified to evaluate the value of such an approach in patients with other complex health conditions.

The intervention was designed to be delivered by trained primary care physical therapists, located in the patient's neighborhood or at their home. This approach has proven to be feasible in the Netherlands, where the primary care physical therapists for the RCT were mainly recruited through a national network with specialized expertise in rheumatic diseases, accessible via www.reumanetnl.nl, but also via other means. The feasibility of such "on-demand" recruitment and training of primary care physical therapists in people with other complex health conditions and/or other countries with different healthcare systems remains to be established.

Cost-effectiveness of longstanding supervised exercise therapy

As economic evaluations of exercise therapy are scarce, in particular in the field of inflammatory arthritis, the cost-effectiveness analysis conducted in the context of the L-EXTRA study adds valuable insights to this research area. The economic analysis presented in Chapter 4 showed that the total intervention costs, the total direct medical costs, and the total societal costs were higher in the longstanding exercise therapy group as compared to usual care in patients with RA and severe functional disability. However, the estimated difference in total societal costs was relatively small, €180 higher in the intervention group compared to the usual care group and with a very broad confidence interval. The net-benefit analysis showed that there was no clear economic preference for either the intervention or usual care: regardless of society's WTP for an additional QALY, both were about equally likely to be cost-effective.

The results of this economic analysis are less favorable than those of the cost-utility analysis of the previously mentioned goal-oriented exercise therapy (Coach2Move) study in frail older adults with mobility limitations [22]. The results of the economic evaluation of that study showed significant cost savings and improved QALYs compared to standard treatment. Notably, in that study, all individuals in the usual care group used physical therapy, whereas in our study the use of physical therapy was left to the discretion of the patient and/or clinicians. Thereby in our study the difference in the use of physical therapy between the two groups was much larger than in the Coach2Move study, making it more difficult to demonstrate the cost-effectiveness of our intervention. One other RCT, that evaluated longstanding (104 weeks, 2 times per week) exercise therapy with usual care in people with RA, yet in those with stable disease [13, 24] showed that usual care was deemed more cost-effective than the longstanding exercise intervention [24]. This conclusion was

based on the higher costs of the intervention, similar QALYs according to the EQ-5D-5L, whereas the QALYs based on the EQ-VAS were more favorable in the usual care group. The differences with the results of our study may be explained by the fact that participants in that study were not selected based on having functional disability (and thus had less room for health benefits) and patients in the intervention group received a fixed amount of 2 weekly sessions over the total period of 2 years, regardless of their individual need for longstanding continuation of supervision, resulting in relatively high intervention costs.

Regarding the cost-effectiveness of physical therapy from a societal perspective, a recent report from the American Physical Therapy Association evaluated the cost-effectiveness of physical therapy across various conditions, including knee osteoarthritis, carpal tunnel syndrome, low back pain, stress urinary incontinence, lateral epicondylitis, vascular claudication, falls prevention, and cancer rehabilitation [34]. The findings indicated that the investigated physical therapist services were both clinically effective and economically beneficial, with the economic benefits of the improvements in patients' quality of life outweighing the net cost of care [25]. Similar conclusions on the societal benefit of physical therapy were drawn in The Netherlands as well (www.Equalis-Substitutiepotentieel-fysio-en-oefentherapie-Eindrapportage-def.pdf).

Strengths and limitations

Methodological strengths of the L-EXTRA study include the randomized, single-blinded controlled study design, the large nationwide sample size, and the low dropout rate. Additionally, the treatment was provided according to a standardized treatment protocol, and all physical therapists delivering the intervention took part in a mandatory training. The assessments consisted of a face-to-face interview, PROMS, and a performance test for the domain physical function. This multifaceted approach significantly enhances the robustness of the findings. Methodological strengths of the L-EXTRA study include the randomized, single-blinded controlled study design, the large nationwide sample size, and the low dropout rate. Additionally, the treatment was provided according to a standardized treatment protocol, and all physical therapists delivering the intervention took part in a mandatory training. The assessments consisted of a face-to-face interview, PROMS, and a performance test for the domain physical function. This multifaceted approach significantly enhances the robustness of the findings.

A limitation of the study was that, due to the focus on longstanding exercise therapy and the possibility to receive it at no additional costs, patients with a relatively positive attitude regarding this therapy may have been overrepresented. This possibly might have affected the external validity, which always is a challenge in RCTs. It raises the question whether the findings are only relevant to patients with a positive attitude towards exercise, or can be generalized to the broader population of RA patients with severe functional limitations.

Another limitation of the study was that patients were aware of their assigned groups, a methodological weakness which cannot be avoided in exercise therapy studies. Blinding always poses a challenge in an RCT evaluating the effectiveness of exercise therapy because the participant and the physical therapist are always aware of whether usual care or the intervention is being administered. Assessments could however be done in a blinded way, although in some cases, despite all efforts for concealment, blinding of assessors for the allocation of patients during assessments proved to be difficult. The rate of concealment failure (69%) was however comparable to another RCT on exercise in RA, where assessors correctly guessed the allocation in 75% of patients [13]. Given the concealment failure in some cases, the possibility that the awareness of the participant influenced the measurements that were carried out by the assessors (PSC and 6MWT) cannot be ruled out.

With respect to treatment fidelity, the amount of information on the content and dosage of treatments that could be analyzed in detail was limited. Due to limited resources available for the review of the records from every treatment session that were handed in by the treating physical therapists, their completeness was checked rather than their content.

Regarding the intervention, the promotion of physical activity was one of its essential elements, and was supported by the provision of a conventional, analog pedometer. The actual usage and satisfaction of patients and physical therapists with this device has been registered but has not yet been analyzed. Here it must be noted that the information we gathered is limited. Overall, the reporting quality of interventions using wearable activity trackers for promoting physical activity in studies in patients with inflammatory arthritis or hip/knee osteoarthritis was found to be moderate to poor [26]. The descriptions were particularly lacking detail with respect to program progression, tailoring, adverse events, and adherence assessment, indicating a need for improved reporting standards [26]. Therefore, in future research, more attention for the accurate description of promotion of

PA using wearable activity trackers in the treatment protocol and the evaluation of the process of delivery and usage and its effectiveness seems warranted.

In our study, patients had access to the intervention over the full duration of the study including the follow-up, and could thus stop or resume treatment at any time, so that permanent discontinuation could only be ascertained in retrospect. The lack of prospective monitoring of the discontinuation is nevertheless a limitation of the study. While according to the protocol the target was 64 sessions in the initial 52 weeks (with 14 optional sessions if needed), the actual average usage was 39 sessions. Twenty-two patients discontinued treatment before completing the intended 52 weeks, possibly indicating that the intervention duration was too lengthy for some, with some patients reaching their treatment goals relatively quickly. Moreover, the impact of the COVID-19 pandemic during the study period may have contributed to this lower usage. Regarding the precise number of treatment sessions it must be noted that discrepancies arose between the number of sessions reported by patients and those recorded by physical therapists, possibly due to recall bias or incomplete registration. Future research should consider more frequent and prospective recording of the number of treatment sessions. With respect to the recording of physical therapy sessions, a clear distinction must be made between the use of the intervention and possible other physical therapy treatments. Despite the lower than expected usage, no conclusions can be drawn about whether shorter interventions would produce comparable results. For such comparisons, a clinical study comparing interventions of different durations would be necessary.

Aim 2: Explore the usage and applicability of various outcome measures to describe the functional ability of people with RA and measures evaluate the effectiveness and safety of exercise therapy in this patient group.

Functional ability

The exercise therapy intervention in the L-EXTRA was aimed at the level of the "Activities and Participation" component of ICF model [18], rather than the potential underlying impairments on the level of 'Body Functions and Structures', such as pain, fatigue, mood, or muscle weakness. The reason was that the role that the contribution of these impairments to individual functional disability and the extent they were addressed in the treatment could vary largely among individuals. Taking this into consideration, outcome measures on the level of limitations in activities and participation were selected as outcome measures to evaluate functional disability (PSC, HAQ-DI and PROMIS PF-10). In this thesis the nature and severity of functional disability of people with RA and severe functional limitations according to these outcome measures, including the PSC (Chapter 5) and the HAQ-DI (Chapter 6) were explored. Furthermore, the usage of PROMIS (Chapter 7) outcome measures in clinical studies in RA and axSpA patients was examined.

PSC

According to the content of the PSC, this thesis identified common limitations in activities prioritized by individuals with RA or axSpA and severe functional disability, using the ICF as a framework (Chapter 5). The most frequent limitations concerned the ICF chapter "Mobility". It was also found that there was substantial overlap between the identified ICF categories in our populations and the contents of the ICF Core Sets for RA and Ankylosing Spondylitis (AS) [27, 28], that describe the aspects of health that are most relevant for patients with these conditions. While overlap with the Core Sets was high, clinicians should note that not all items in these Core Sets may be as prevalent in clinical practice, whereas some limitations patients are experiencing may not be in the ICF Core Sets. In addition to working with standardized lists of possibly relevant activities, the elicitation and prioritization of individual limitations by means of a patient-specific instrument such as the PSC may be of added value. However, it has been noted in previous research that the descriptive properties and psychometric quality of patient-specific instruments for physical functioning, such as the PSC or MACTAR, are only partly investigated [29]. Here it must be noted that patient-specific instruments are usually administered by means of a face-to-face

interview and are thus time consuming, which is an important drawback in the context of research. The development of versions of those instruments that can be completed by patients without a professional could be a worthwhile direction in order to better implement the use of patient-specific measures in research.

HAQ-DI

The HAQ-DI is, in contrast with patient-specific measures, an instrument with a fixed list of activities [30, 31]. Most patients in the L-EXTRA study had a HAQ-DI total score corresponding to moderate to severe disability. On the level of the HAQ-DI domains, most patients had limitations in multiple domains, with the domains "Usual activities", "Personal hygiene" and "Reaching" showing the highest proportions of patients with the worst scores (Chapter 5). These findings suggest limitations across multiple domains, despite the observation that some of the 20 activities in the HAQ-DI may seem a little outdated and not all activities may be pertinent to each patient. An example of an activity that may nowadays be less challenging includes the use of taps, which are mostly long handled in many countries. On the other hand, the HAQ-DI does not include the use of a smartphone or the keyboard of a computer or laptop, which activities are currently very common for many people. Additionally, it remains unclear if the activities where a patient indicates to have most difficulties are also deemed most relevant for this individual patient. To gain more insight into the impact of specific limitations in the HAQ-DI, a previous study developed a version where the patients had to rate the importance of each of the 20 activities addressed by the HAQ-DI, and to select the 5 activities they considered the most important (individualized scales) [32]. From that study it was concluded that individualized scales had similar measurement properties as the HAQ-DI, whereas the additional measuring of importance gave complementary information to the measure of disability. The study stated that "even if individualization is probably not needed for group assessment in all randomized controlled trials, the use of individualized questionnaires could be clinically relevant for individual RA patients" [32]. In our study, higher (worse) HAQ-DI scores were associated with advanced age, longer disease duration, not being employed, having one or more joint arthroplasties, and worse outcomes for daily functioning and physical quality of life, but not with higher disease activity. This finding emphasizes the need for comprehensive assessments in the monitoring of the disease course, and not merely focus on disease activity.

PROMIS

The PROMIS® measures were developed to create standardized, precise, and efficient assessments of PROMs across various health conditions and populations. In the L-EXTRA study the PROMIS PF-10 was used. As knowledge on the use of the PROMIS PF-10 in clinical trials in rheumatology was scarce, a systematic literature review was performed (Chapter 7), from which it was concluded that PROMIS measures are relatively infrequently employed in recent clinical studies in people with RA. Regarding the specific PROMIS measures that were used, the diversity in measures and versions was considerable. Regarding the limited usage, it must be noted that their use is sparsely recommended in Core Sets for outcome assessments in clinical trials in inflammatory arthritis. The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) core domain set for RA [33] and the ICF Core Sets for RA/AS [27, 28] do not recommend the use of any specific measurement instrument. Recently, in line with the Assessment of SpondyloArthritis international Society (ASAS)-OMERACT core domain set for axSpA [34] a set of specific measurement instruments has been proposed [35], but this does not include PROMIS measures.

In contrast, the International Consortium for Health Outcome (ICHOM) Set of Outcomes That Matter to People Living With Inflammatory Arthritis [36] does comprise specific measurement instruments, some of which concern PROMIS measures: the PROMIS General Health, PROMIS Pain Interference, PROMIS Physical Function and PROMIS Fatigue. In our systematic review on the use of PROMIS in clinical trials, we observed that several PROMIS measures other than those recommended by ICHOM [36] were relatively frequently reported, including the PROMIS Sleep Disturbance, PROMIS Abilities to Participate in Social Roles and Activities, PROMIS Depression, and PROMIS Anxiety. These measures may not be in the ICHOM Core Set for Inflammatory Arthritis but do align with the general health domains as proposed by the OMERACT and ASAS-OMERACT [33-34]. If the application of a PROMIS instrument is being considered or advised, the observed variation in versions and instruments suggests that standardization of its use is crucial for future research to enable meaningful comparisons among studies.

Safety of exercise

Previous systematic reviews on the effectiveness of exercise therapy in RA or axSpA suggested its safety, but it was also mentioned that some aspects of safety were inadequately described in the trials considered. This thesis presents a systematic literature review that further explored the quality of reporting of harms in RCTs on supervised exercise therapy in RA or axSpA, showing that 50–75% of studies lacked information on harms outcomes, and, if provided, did not present details on how harms were defined or monitored. The overall inadequacy of the reporting of harms indicates a critical need for improvement. The review suggested the need for the establishment of consensus on the selection of relevant harms outcomes and their measurement in exercise trials, incorporating prespecified thresholds where applicable. Moreover, better adherence to existing recommendations for their reporting is needed, in particular the CONSORT Harms 2022 Checklist. For harms in rheumatology clinical trials in general, there are a number of recent and current initiatives, developed in collaboration with the OMERACT community [37-39]. These initiatives aim to increase the understanding of the concept of safety/harms experienced by patients involved in clinical trials in the field of rheumatic and musculoskeletal diseases [37], identify harm domains from existing outcome measurements in rheumatology [38], and to develop and validate a checklist of potential safety events for use in rheumatology clinical trials [39]. If such a checklist is available in the future, its usefulness for exercise trials can be further established.

Strengths and Limitations

The strengths of Chapters 5 and 6 lie in the fact that data from a substantial sample of RA and axSpA patients with severe functional disability were used, who are usually excluded from exercise trials). In Chapter 5, we linked the content of PSC goals that were derived from patients with RA and axSpA and severe functional disability in the primary care setting to the ICF, thereby focusing solely on the "Activities and Participation" component. In patients with RA the contents of rehabilitation goals have been linked to the ICF in a similar way as in the study in Chapter 5 [40], yet this was done using other methods for goal setting than the PSC and in the rehabilitation setting. In Chapter 6, the nature and extent of functional disability in patients with RA was explored using the HAQ-DI. The fact that the analyses were done across its eight domains was a unique feature of this study, in addition to the fact that it was done in the specific subgroup with severe functional disability.

There are a number of limitations regarding the studies outlined in Chapters 5 and 6. Primarily, as these studies focused on baseline data from RCTs with a specific selection process, their findings may not be broadly applicable to all individuals with RA or axSpA and severe functional disability. Moreover, it is conceivable that the nature of functional limitations may be different in RA individuals who have an overall better level of physical functioning. This does not necessarily mean that their limitations have less impact: they may pertain to different activities and/or are on another level. Here, it must be kept in mind that in order to function and participate properly and fully in our society, the demands are constantly changing and increasing in some respects. Another observation that is relevant with respect to the generalizability of the findings relates to the relatively high proportion of females (90%) and patients with multiple comorbidities (96%) within the study population. Research indicates that men with RA are significantly underrepresented in RCTs as compared to the total population of RA patients [41]. Additionally, studies suggest that females tend to experience a more severe disease course with higher disease activity, leading to greater disability [42]. However, it remains to be established if and to what extent severe functional disability is more common among women than men with RA and/or that women are more likely to participate in clinical trials in general.

Regarding the exploration of the use of PROMIS measures in clinical research in inflammatory arthritis, the main strengths of the review in Chapter 7 were that it provided a comprehensive overview of the utilization and outcomes of PROMIS measures in different contexts and populations, thus enriching the depth and scope of the study's findings. To our knowledge this is the first study to evaluate the use of these measures in patients with inflammatory arthritis specifically. A limitation of the systematic review was that the significant variability with respect to the types and versions of the PROMIS instruments employed in clinical trials in RA and axSpA precluded meaningful comparisons across populations or meta-analysis. Moreover, the number of identified studies in people with axSpA was relatively low as compared to RA studies, so that a separate interpretation was not possible.

The strengths of Chapter 8 lie in its focus on RCTs assessing supervised exercises in adults with RA or axSpA, ensuring a meticulous selection process for pertinent studies. Additionally, the detailed extraction of harm data according to the CONSORT Harms 2022 Checklist [43] offered a structured and standardized method to evaluate reporting quality and the types of reported harms within the included studies. Notably, this study contributed significantly to the existing body of evidence by being the first to comprehensively report on the quality and nature of harms in patients with RA and axSpA. A limitation of the review was that a meta-analysis was not deemed feasible due to insufficient reporting of harms outcomes in most studies. In addition, our elaboration of harms outcomes was dependent on the level of detail of the data collection in the methods section(s), which could potentially impact the comprehensive understanding of the nature of harms outcomes. Additional limitations arise from the focus on English-language studies, possibly resulting in the omission of relevant non-English studies.

Implications for clinical practice and future research

In conclusion, the evidence presented in this thesis demonstrates the effectiveness of longstanding, personalized, supervised active exercise therapy in enhancing functional ability and overall quality of life for individuals with RA and severe functional disability. The intervention showed superior outcomes compared to standard care, and the economic analysis indicated that despite slightly higher costs, there are no economic reasons to refrain from the implementation of the intervention. The L-EXTRA study has highlighted the feasibility and effectiveness of an exercise therapy intervention ensuing a comprehensive approach, which integrates assessment, goal-setting, collaborative treatment planning, active exercises, education/support, and regular monitoring/evaluation for patients with complex RA and multimorbidity, and its delivery by primary care physical therapists. To ensure a proper delivery of this intervention, it is crucial for physical therapists to be adequately trained.

As a result of these findings the National Health Care Institute (Zorginstituut Nederland) advised positively to the Minister of Health, Welfare and Sport regarding the reimbursement of this physical therapy intervention delivered by trained professionals from the basic health insurance for this subgroup of RA patients [44]. The Minister of Health, Welfare and Sport has accepted this recommendation, which means that as of 1 January 2025, longstanding personalized supervised active exercise therapy for people aged 18 and older with RA and severe functional limitations will be reimbursed by the basic health insurance package, with reimbursement starting from the first treatment and without a limit on the number of treatments.

For the ultimate implementation of the intervention in case of a positive decision from the minister, a number of insights are needed. First of all, the size of the population with severe functional limitations has so far only been estimated by an expert group to be 5% of people with RA. A more precise estimation based on a large, random sample and utilizing the indication criteria as applied in the studies is needed. Additionally, the extent of long-term use of exercise therapy other than the intervention employed in the trial must be explored. Longstanding usage may not be uncommon, and may, in part be related to the insurance status of patients [45], whereas it is unknown to what extent patients are fulfilling the criteria for longstanding, active treatment as used in the trial. A more elaborate exploration of the content of physical therapy treatment in those patients may reveal if, apart from

implementation strategies, also activities concerning de-implementation of specific treatment modalities, such as passive therapies as monotherapy, are needed. Data on the accessibility of exercise therapy are also lacking, particularly regarding the number of people with RA who require exercise therapy but encounter barriers to accessing it, including financial barriers in case of no or limited additional health insurance coverage. Apart from quantitative information, it is also important to gain more insight in the perspectives of all stakeholders regarding the future access to and delivery of the intervention. These include their perspectives on the professional education and training for physical therapists to deliver the intervention, their registration and visibility, the organization of the screening for eligibility, and an overall view on appropriate care including indications for long-term physical therapy as opposed to those for short-term interventions.

These insights will facilitate the planning for upscaling activities, including informing patients, rheumatologists, nurse specialists and physical therapists, and the training and registration of physical therapists delivering the intervention. This training should also include the screening of patients with respect to their eligibility for the intervention. Given the valuable insights gained from the L-EXTRA study and recognizing the complexities of implementing exercise therapy interventions in real-world settings, an implementation study addressing all of the abovementioned issues is currently being carried out [46].

Ideally the abovementioned implementation activities should have been carried out during the conduct of the trial, as is the case in studies with a so-called Effectiveness-implementation hybrid study design [47, 48]. Such an integrated approach aims to proactively address challenges that may arise during the intervention implementation, allowing for real-time problem-solving and efficiency gains instead of addressing these issues after the trial is conducted [47, 48]. However, given the limited resources for the conduct of the study, activities related to the future implementation could only be sparsely carried out.

The preceding paragraphs centered on the national implementation in The Netherlands. However, on an international scale, healthcare services exhibit considerable variability. The availability of primary care physical therapy may differ across countries, influenced by factors such the labor market for physical therapists, their competences and education levels, and national treatment reimbursement policies. In some countries, hospitals or rehabilitation centers may offer multidisciplinary services for the specific cohort of patients with RA and severe disability.

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Chapter 10

Dutch summary (Nederlandse samenvatting)

Samenvatting

Reumatoïde artritis (RA) is een vorm van inflammatoire artritis, resulterend in functionele beperkingen bij een aanzienlijk deel van de patiënten. Om functionele beperkingen bij mensen met RA te voorkomen is oefentherapie een veelvoorkomende behandelingsoptie, die wordt aanbevolen in professionele richtlijnen. Deze aanbevelingen zijn gebaseerd op bewijs voor de effectiviteit van oefentherapie bij RA in meerdere klinische studies. Deze studies werden echter allemaal uitgevoerd bij mensen met RA met een relatief gunstige gezondheidsstatus. Hierdoor ontbreekt bewijs voor de (kosten)effectiviteit van oefentherapie bij mensen met RA en ernstige functionele beperkingen ontbrak. Ernstige functionele beperkingen kunnen voortkomen uit bijvoorbeeld aanhoudende, hoge ziekteactiviteit, gewrichtsschade, complicaties van de ziekte of de behandeling, of comorbiditeit. Naast het gebrek aan kennis over de (kosten)effectiviteit van oefentherapie in deze specifieke subgroep, waren er ook kennishiaten met betrekking tot de optimale uitkomstmaten voor de evaluatie van dagelijks functioneren en de veiligheid van oefentherapie bij mensen met RA. Om deze kennishiaten te adresseren, richt het eerste deel van dit proefschrift zich op de evaluatie van de effectiviteit en kosteneffectiviteit van een langdurige, gepersonaliseerde, gesuperviseerde, actieve oefentherapie-interventie vergeleken met gebruikelijke zorg bij patiënten met RA met ernstige functionele beperkingen (Hoofdstukken 2-4). In het tweede deel worden het gebruik en de toepasbaarheid van verschillende uitkomstmaten met betrekking tot de effectiviteit en veiligheid van oefentherapie bij RA onderzocht (Hoofdstukken 5-8).

Hoofdstuk 1 beschrijft de epidemiologie en pathofysiologie van RA en de impact ervan volgens de verschillende dimensies van de International Classification of Functioning, Disability and Health (ICF). Het farmacologische en niet-farmacologische management van RA in Nederland wordt besproken, met de nadruk op de rol van oefentherapie. Daarnaast wordt een overzicht gegeven van uitkomstmaten voor de evaluatie van dagelijks functioneren bij mensen met RA, evenals van de kwaliteit van het vastleggen van mogelijke ongewenste neveneffecten in onderzoeken naar oefentherapie bij RA.

Hoofdstuk 2 beschrijft de protocollen van twee parallelle, gerandomiseerde klinische onderzoeken (RCTs) naar oefentherapie bij mensen met RA of axiale spondyloartritis (axSpA), waarbij de L-EXTRA (Longstanding EXercise Therapy in patients with Rheumatoid Arthritis) studie de primaire focus van dit proefschrift is. Het protocol van de

L-EXTRA studie betreft een enkelvoudig geblindeerde RCT naar de (kosten)effectiviteit van langdurige, gepersonaliseerde, actieve oefentherapie in vergelijking met gebruikelijke zorg bij mensen met RA en ernstige functionele beperkingen. De studie beoogde in totaal 215 deelnemers te includeren. De interventie, uitgevoerd door getrainde fysiotherapeuten in de eerste lijn, omvatte het stellen van individuele doelen, actieve oefeningen, educatie en zelfmanagementondersteuning met betrekking tot fysieke activiteit. Het primaire eindpunt voor effectiviteit was de verandering in de met de Patiënt Specifieke Klacht (PSK) gemeten door de patiënt hoogst geprioriteerde functionele beperking (PSK1) na 52 weken. Secundaire eindpunten omvatten PSK-activiteiten gerangschikt als 2 en 3, de Health Assessment Questionnaire-Disability Index (HAQ-DI), de Patient-Reported Outcomes Measurement Information System Physical Function 10-item (PROMIS PF-10), de Rheumatoid Arthritis Quality of Life vragenlijst (RAQoL), de 6-minuten wandeltest (6MWT), en de Short Form-36 Physical and Mental Component Summary Scales (SF-36 PCS en MCS). Bijwerkingen (Adverse Events, AEs) die (mogelijk) verband hielden met de interventie werden prospectief geregistreerd in de interventiegroep door de behandelende fysiotherapeuten. Voor de kosteneffectiviteitsanalyse werden de EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) en de EuroQol-Visuele Analoge Schaal (EQ-VAS) gebruikt om utiliteiten en quality-adjusted life years (QALYs) te bepalen. Bovendien werden vragenlijsten over het gebruik van gezondheidszorg en werk afgenomen bij baseline, en na 12, 26 en 52 weken.

Hoofdstuk 3 presenteert de resultaten van de effectiviteit tot en met 52 weken. Tussen maart 2020 en december 2021 werden in totaal 217 geschikte deelnemers geïncludeerd. Na de randomisatie trokken twee deelnemers zich onmiddellijk terug (één uit elke groep) en zij werden vervangen om het beoogde totaal van 215 deelnemers te bereiken (109 interventiegroep, 106 gebruikelijke zorggroep). Elf deelnemers (4 interventiegroep (4%), 7 gebruikelijke zorggroep (7%)) vielen tussen baseline en 52 weken uit. In de interventiegroep begonnen 104 deelnemers (95%) met de interventie, gemiddeld gebruikmakend van 39 sessies (SD 15.9). Ook ontvingen 70 (66%) deelnemers in de gebruikelijke zorggroep fysiotherapie tijdens de 52 weken durende studieperiode. Deze fysiotherapie werd gegeven naar inzicht van de eigen fysiotherapeut en was anders dan de studie-interventie. Na 52 weken was de verbetering in de PSK1 significant groter in de interventiegroep (gemiddeld verschil [95% betrouwbaarheidsinterval (BI)] -1.7 [-2.4; -1.0]). Alle secundaire uitkomsten vertoonden ook significant grotere verbeteringen in de interventiegroep, behalve de SF-36

MCS. Slechts één milde, voorbijgaande AE deed zich voor in de interventiegroep. Concluderend, na 1 jaar bleek langdurige, gesuperviseerde oefentherapie effectiever dan gebruikelijke zorg bij personen met RA en ernstige functionele beperkingen wat betreft fysiek functioneren en fysieke kwaliteit van leven.

Hoofdstuk 4 beschrijft de economische analyse van de studie gepresenteerd in Hoofdstukken 2 en 3. De kostenutiliteitsanalyse werd uitgevoerd vanuit het maatschappelijk perspectief met een follow-up van één jaar. Verschillen in kosten en QALYs werden geanalyseerd volgens het intention-to-treat principe met behulp van kosteneffectiviteit 'acceptability curves'. De gemiddelde directe kosten van de interventie waren €1.423 per deelnemer in de interventiegroep. De totale medische kosten in de studieperiode van één jaar waren €754 (95% BI €-3012 tot €4519) hoger in de interventiegroep dan de gebruikelijke zorggroep, welk verschil niet-statistisch significant was. De totale maatschappelijke kosten over de studieperiode waren ook niet-significant hoger in de gebruikelijke zorggroep, met een klein verschil van €180 (95% BI €-4493 tot €4852). De QALYs waren niet-significant hoger in de interventiegroep dan in de gebruikelijke zorggroep, met een verschil 0.02 voor de EQ-5D-5L (95% BI -0.05 tot 0.09) en 0.04 voor de EQ-VAS (95% BI 0.00 tot 0.08). Bij een Willingness-To-Pay drempel van €50000 per QALY was, met 60% zekerheid, de interventie een kosteneffectieve strategie. Concluderend, ondanks de enigszins hogere kosten in de interventiegroep, maar gezien de betere klinische resultaten, suggereren de resultaten van deze studie dat er geen economische redenen zijn om af te zien van langdurige, gepersonaliseerde, actieve oefentherapie bij mensen met RA en ernstige functionele beperkingen.

Patiëntspecifieke uitkomstmaten bieden inzicht in de aard en ernst van specifieke beperkingen die worden ervaren door de individuele patiënt. Dergelijke instrumenten kunnen niet alleen ondersteuning bieden bij het stellen van gepersonaliseerde doelen bij revalidatie-interventies, waaronder oefentherapie, maar kunnen ook worden gebruikt als uitkomstmaten in klinische studies. De eerdergenoemde PSK is een voorbeeld van zo'n patiëntspecifieke uitkomstmaat, en bleek in eerdere onderzoeken veranderingen in de ervaren beperkingen bij het functioneren en/of de participatie in de tijd te kunnen detecteren. De PSK wordt afgenomen via een face-to-face interview en identificeert de drie voor de patiënt meest revelante activiteiten waarbij een beperking wordt ervaren, waarbij

de moeilijkheidsgraad van elke activiteit wordt gescoord van 0 = geen moeite tot 10 = onmogelijk om te doen.

Met behulp van de informatie uit de PSK die werd afgenomen in de trial beschreven in Hoofdstukken 2-4, beoogde de studie in **Hoofdstuk 5** de drie als hoogst geprioriteerde functionele beperkingen van mensen met RA of axSpA te beschrijven. Hiertoe werden de baselinegegevens van 206 RA- en 155 axSpA-deelnemers aan het gerandomiseerde gecontroleerde onderzoek beschreven in Hoofdstukken 2, 3 en 4, en het parallelle onderzoek bij axSpA, geanalyseerd. Voor elke patiënt werden de drie meest beperkende activiteiten verkregen uit de PSK gekoppeld aan overeenkomstige gecodeerde tweede of derde graads ICF-categorieën met behulp van gestandaardiseerde methodologie. De frequenties van waargenomen ICF-categorieën werden berekend en vergeleken met de Activiteiten en Participatie-items van de ICF Core Sets voor RA (32 tweede graads-categorieën) en Ankylosing Spondylitis (AS) (24 tweedegraads-categorieën). ICF Core Sets omvatten die ICF-categorieën die als meest relevant worden beschouwd voor mensen met een specifieke aandoening en bestaan zowel uit een uitgebreide als een beknopte versie. De resultaten van de studie toonden aan dat zowel voor RA als voor axSpA de meest genoemde beperkingen in de PSK gerelateerd waren aan het ICF-hoofdstuk “Mobiliteit”, waarin activiteiten zoals “Lopen”, “Veranderen van basale lichaamshouding”, “Traplopen”, “Grijpen”, “Tillen” en “Handhaving van staande houding” zijn opgenomen. Een aanzienlijk deel van de hoogst geprioriteerde activiteiten kwam overeen met die in de uitgebreide en beknopte ICF Core Sets voor RA en AS. Dertien activiteiten (vier bij RA en negen bij axSpA) werden gevonden buiten de categorieën die zijn opgenomen in de uitgebreide Core Sets voor RA en AS, waaronder “Traplopen” bij RA en “Fijn handgebruik” bij axSpA, die door meer dan 5% van de onderzoekspopulaties werden genoemd.

Anders dan de PSK, is de HAQ-DI een gestandaardiseerde vragenlijst die de moeite met het uitvoeren van 20 specifieke activiteiten, gecategoriseerd in acht domeinen, beoordeelt (Aankleden & Verzorging, Opstaan, Eten, Lopen, Hygiëne, Reiken, Grijpkracht, Activiteiten). De scores van de items variëren van 0-3 (0 zonder enige moeite tot 3 onmogelijk uit te voeren), terwijl het gebruik van hulp van een andere persoon of hulpmiddel kan worden meegerekend in de score. De domeinscores variëren van 0 tot 3, en de totaalscore van 0–3, waarbij 0-1 (licht), >1–2 (matig-ernstig), en >2–3 (ernstig-zeer ernstig). De resultaten van de HAQ-DI worden meestal gerapporteerd als de totaalscore.

Hoofdstuk 6 had tot doel de aard en ernst van functionele beperkingen bij mensen met RA en ernstige beperkingen te beschrijven aan de hand van de HAQ-DI. Hiertoe werden de baselinegegevens van 215 deelnemers aan de L-EXTRA-studie beschreven in Hoofdstukken 2, 3 en 4 geanalyseerd. Om de associaties tussen de HAQ-DI-score aan de ene kant en patiëntkenmerken en andere uitkomstmaten aan de andere kant te bepalen, werden de patiëntkenmerken en andere uitkomstmaten vergeleken tussen patiënten met een HAQ-DI-score <2 en ≥2, met behulp van de Student's t-toets of de Chi-kwadraat toets. De gemiddelde HAQ-DI-score van de 215 deelnemers was 17 (SD 0,5). Meer dan de helft van de deelnemers (n=120; 56%) had een HAQ-DI-domeinscore ≥1 in alle domeinen, en 170 (79%) hadden een score ≥1 in 7 of alle 8 HAQ-DI-domeinen. Ernstige beperkingen kwamen het meest voor in de domeinen "Activiteiten", "Grijpen", "Reiken" en "Hygiëne", waarbij 75% of meer van de onderzoekspopulatie een domeinscore van ≥2 had. Mensen met hogere HAQ-DI-scores waren significant ouder, hadden een langere ziekteduur, hadden vaker geen betaalde baan en hadden vaker één of meer gewrichtsvervangende operaties dan degenen met lagere HAQ-DI-scores. Uit dit onderzoek werd geconcludeerd dat de meerderheid van patiënten met RA en ernstige functionele beperkingen beperkingen ervaarden in (bijna) alle HAQ-DI-domeinen. De HAQ-DI-score was geassocieerd met verschillende sociodemografische kenmerken en andere uitkomstmaten voor fysiek functioneren.

De zogenaamde PROMIS® set van meetinstrumenten omvat een reeks persoonsgerichte uitkomstmaten die zijn ontwikkeld om de fysieke, mentale en sociale gezondheid van volwassenen en kinderen te evalueren en te monitoren. PROMIS-instrumenten kunnen zowel worden gebruikt in de algemene bevolking als bij mensen met specifieke aandoeningen. PROMIS-instrumenten leveren gestandaardiseerde scores op, uitgedrukt als T-scores, gerelateerd aan scores in de algemene bevolking. PROMIS-instrumenten bleken in eerdere onderzoeken een grotere precisie te hebben dan de meeste conventionele uitkomstmaten, waardoor de efficiëntie van klinische onderzoeken wordt verhoogd. Hoewel PROMIS-instrumenten waarschijnlijk ook van waarde zijn in onderzoek bij mensen met inflammatoire artritis, is er weinig bekend over hun daadwerkelijke gebruik in klinische studies.

In **Hoofdstuk 7** wordt een systematische literatuurreview beschreven die het gebruik en de resultaten van PROMIS-instrumenten in klinische studies bij mensen met RA of axSpA onderzoekt. Het literatuuronderzoek werd uitgevoerd in negen elektronische databases, en was gericht op publicaties vanaf het jaar 2007, toen PROMIS werd geïntroduceerd. In de review werden alle oorspronkelijke, klinische studies bij patiënten met RA en/of axSpA die het gebruik van een of meer PROMIS-instrumenten rapporteerden opgenomen. De selectie van studies en extractie van gegevens werd uitgevoerd door twee onderzoekers. In totaal voldeden 29 studies (25 voor RA, 3 voor axSpA, en 1 voor beide) aan de inclusiecriteria. Er werden twee algemene PROMIS-instrumenten (PROMIS Global Health, PROMIS-29) en 13 domein-specifieke PROMIS-instrumenten gerapporteerd, waarbij de PROMIS Pain Interference, Physical Function (inclusief de PROMIS PF-10), Fatigue, en Depression het meest frequent werden gebruikt. De resultaten gaven aan dat de gezondheidsstatus van deelnemers aan deze studies over het algemeen slechter was dan het gemiddelde van de algemene populatie. Er was niet aanzienlijke variabiliteit in het gebruik van verschillende PROMIS-instrumenten maar ook in de verschillende versies van één instrument. Dit onderstreept de noodzaak tot meer standaardisatie van het gebruik van PROMIS-instrumenten in klinisch onderzoek bij mensen met RA of axSpA om zinvolle vergelijkingen tussen studies mogelijk te maken.

Klinische beslissingen over interventies in de gezondheidszorg worden meestal gebaseerd op het juiste evenwicht tussen de verwachte gewenste gezondheidsvoordelen en mogelijke ongewenste effecten. De kennis over mogelijke schadelijke effecten van oefentherapie bij inflammatoire artritis is echter relatief beperkt. In **Hoofdstuk 8** wordt een systematische literatuurreview gepresenteerd die de kwaliteit van de rapportage en de aard van de schadelijke effecten beschrijft in klinische studies die de effectiviteit van gesuperviseerde oefentherapie onderzochten bij patiënten met RA of axSpA. De review omvatte RCTs bij volwassenen met RA of axSpA waarbij oefentherapie (aerobe, spierversterkende, flexibiliteit of range of motion, neuromotorische, of mind-body-oefeningen) met minstens zes gesuperviseerde behandelsessies werd vergeleken met een controlegroep. Om deze studies te identificeren werd een zoekstrategie met sleutelwoorden gerelateerd aan RA en axSpA, oefentherapie en mogelijke nadelige neveneffecten zoals (spier)pijn of uitputting toegepast in acht databases, tot februari 2023. In totaal werden 40 RCTs bij RA en 25 bij axSpA geselecteeerd, waarvan er 29 (73%) en 13 (52%) enige informatie over nadelige effecten rapporteerden. Slechts 13 (33%) van de RCTs bij RA en 4 (16%) van de RCTs bij

axSpA gaven details over het verzamelen van uitkomsten voor mogelijke nadelige effecten in de methode sectie. Vooraf gespecificeerde nadelige uitkomsten werden beschreven in 8 (20%) RCTs bij RA en 2 (8%) bij axSpA, terwijl niet-vooraf gespecificeerde nadelige uitkomsten werden beschreven in respectievelijk 6 (15%) en 4 (16%) RCTs. Vooraf gespecificeerde nadelige uitkomsten omvatten verschillende uitkomstmaten voor pijn, ziekteactiviteit, ontsteking en gewrichtsschade. Niet-vooraf gespecificeerde schadelijke uitkomsten varieerden sterk, waarbij pijn het meest frequent gerapporteerd werd. Gezien de over het algemeen slechte kwaliteit van de rapportage van ongewenste effecten van oefentherapie wordt het beter gebruik van de Consolidated Standards of Reporting Trials (CONSORT) Harms 2022 Checklist, met aandachtspunten voor de planning, uitvoering en rapportage van de meting van nadelige effecten in klinische trials aanbevolen.

Implicaties voor de klinische praktijk en toekomstig onderzoek

In dit proefschrift is beschreven dat langdurige, gepersonaliseerde, gesuperviseerde actieve oefentherapie effectiever is dan gebruikelijke zorg ten aanzien van het dagelijks functioneren en de fysieke kwaliteit van leven voor mensen met RA en ernstige functionele beperkingen. De economische analyse gaf aan dat ondanks de enigszins hogere kosten, er geen economische redenen zijn om af te zien van de implementatie van de interventie.
Op basis van deze bevindingen heeft het Zorginstituut Nederland een positief advies uitgebracht aan de Minister van Volksgezondheid, Welzijn en Sport met betrekking tot de vergoeding van deze fysiotherapie-interventie, geleverd door getrainde professionals, vanuit de basiszorgverzekering voor deze subgroep van RA-patiënten. De Minister van Volksgezondheid, Welzijn en Sport heeft dit advies overgenomen, waarmee langdurige gepersonaliseerde gesuperviseerde actieve oefentherapie bij mensen van 18 jaar en ouder met RA en ernstige functionele beperkingen vanaf 1 januari 2025 definitief wordt vergoed vanuit het basispakket van de zorgverzekering, met een vergoeding vanaf de eerste behandeling en zonder maximum voor het aantal behandelingen.

Voor de uiteindelijke implementatie van de interventie in de dagelijkse praktijk moeten er nog een aantal stappen worden gezet. Allereerst moet worden vastgesteld wat de precieze omvang van de populatie met ernstige functionele beperkingen is; tot nu toe is deze door een expertgroep geschat op 5% van de totale groep van mensen met RA.

Daarnaast moet onderzoek naar de omvang en inhoud van de huidige fysiotherapeutische behandeling in de dagelijkse praktijk waardevolle informatie opleveren zowel wat betreft het implementeren van de kernelementen van de langdurige, gepersonaliseerde en actieve interventie, als voor deïmplementatie van behandelingen waarvan de effectiviteit in deze patiëntengroep niet is bewezen zoals langdurige passieve therapieën als monotherapie. Ook ontbreken gegevens over de toegankelijkheid van oefentherapie, met name met betrekking tot het aantal mensen met RA die korter of langer oefentherapie nodig hebben maar (financiële) belemmeringen ondervinden bij de toegang ertoe. Naast kwantitatieve informatie is het ook belangrijk om meer inzicht te krijgen in de perspectieven van alle belanghebbenden (o.a. mensen met RA, fysiotherapeuten en oefentherapeuten, reumatologen, zorgverzekeraars, richtlijnontwikkelaars, scholingsaanbieders) met betrekking tot toekomstige toegang tot en levering van de interventie

Deze inzichten zullen het ontwikkelen van een implementatiestrategie vergemakkelijken. De implementatiestrategie omvat onder andere het informeren van patiënten, reumatologen, verpleegkundig specialisten en fysio- en oefentherapeuten en het trainen en registreren van fysio- en oefentherapeuten die de interventie uitvoeren. Deze registratie is belangrijk vanuit kwaliteitsoogpunt, maar ook om de gekwalificeerde behandelaren vindbaar te maken voor patiënten en verwijzers. Op dit moment wordt een voorbereidende implementatiestudie uitgevoerd die zich richt op de hierboven genoemde aspecten. Idealiter zouden de hierboven genoemde implementatieactiviteiten al tijdens de uitvoering van de studie hebben plaatsgevonden, zoals het geval is bij studies met een zogenaamd effectiviteit-implementatie hybride studie design. Echter, gezien de beperkte middelen voor de uitvoering van de studie, konden behalve een beknopte procesevaluatie geen uitgebreidere activiteiten met betrekking tot de toekomstige implementatie worden uitgevoerd.

De voorgaande alinea's richtten zich op de toekomstige implementatie in Nederland. Op internationaal niveau vertonen zijn gezondheidszorgsystemen sterk verschillend. De beschikbaarheid van eerstelijns fysiotherapie kan verschillen tussen landen, bijvoorbeeld omdat er variatie is in de competenties, opleidingsniveaus en de arbeidsmarkt van fysiotherapeuten of de vergoeding van de behandelingen. In sommige landen wordt fysiotherapie voor mensen met RA en ernstige functionele beperkingen, anders dan in Nederland het geval is, voornamelijk in ziekenhuizen of revalidatiecentra aangeboden.

11

Chapter 11

Appendices
(Bibliography, Curriculum Vitae, Acknowledgements)

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Scientific papers

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Abstracts

A. European Alliance of EULAR (European Alliance of Associations for Rheumatology) Annual congress, June 2024, Vienna, Austria.
    1. Teuwen MMH, van Weely SFE, van den Ende CHM, van Wissen MAT, Vliet Vlieland TPM, Peter WF, den Broeder AA, van Schaardenburg D, Gademan MGJ, van den Hout WB. Cost-utility analysis of longstanding exercise therapy versus usual care in people with rheumatoid arthritis and severe functional limitations. **(Oral presentation)**.

B. American College of Rheumatology (ACR) Convergence 2023, November 2023, San Diego, United States.
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D. EULAR (European Alliance of Associations for Rheumatology) Annual congress, June 2023, Milan, Italy.

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   1. Van Wissen MAT, **Teuwen MMH**, van den Ende CHM, Vliet Vlieland TPM, den Broeder AA, van den Hout WB, Peter WF, van Schaardenburg D, van Tubergen AM, Gademan MGJ, van Weely SFE. Effectiveness and cost-effectiveness of longstanding exercise therapy versus usual care in patients with axial spondyloarthritis or rheumatoid arthritis: the protocols of two parallel randomized controlled trials. Published in: Annals of the Rheumatic Diseases 2021;80:1460-1461. **(Published online)**.

Curriculum Vitae

Max Teuwen werd geboren op 17 september 1994 in Haarlem. Na het behalen van zijn Atheneumdiploma aan de Katholieke Scholengemeenschap Hoofddorp, begon hij in 2014 met de opleiding Fysiotherapie aan de Saxion Hogeschool Enschede. Na succesvol zijn Bachelor te hebben afgerond in Juli 2018, Max vervolgde zijn studie aan de Vrije Universiteit Amsterdam, waar hij in juli 2019 zijn Master in Musculoskeletale Fysiotherapiewetenschappen voltooide in juli 2019. Na het succesvol afronden van zijn masterthesis bij de afdeling Orthopaedie van het Onze Lieve Vrouwe Gasthuis in Amsterdam, bleef hij op deze afdeling actief als onderzoeksassistent tussen december 2018 en december 2019. In januari 2020 begon hij aan zijn promotietraject bij het Leids Universitair Medisch Centrum op de afdeling Orthopaedie, Revalidatie en Fysiotherapie onder leiding van prof. dr. Thea Vliet Vlieland, dr. Salima van Weelij, dr. Els van den Ende en dr. Maaike Gademan. Tussen januari 2020 en januari 2024 was Max de uitvoerende onderzoeker van de in dit proefschrift beschreven studie naar het effect van actieve, gepersonaliseerde oefentherapie bij mensen met reumatoïde artritis en ernstige functionele beperkingen. Hij was verantwoordelijk voor het werven van 215 deelnemers, het verzamelen en analyseren van gegevens, het mede coördineren en plannen van de studie, en het begeleiden van zowel de deelnemende patiënten als fysiotherapeuten. Zijn taken omvatten ook het schrijven van wetenschappelijke artikelen en abstracts, het presenteren van onderzoek op internationale congressen en binnen ziekenhuisafdelingen. Na het afronden van zijn promotietraject is hij in mei 2024 aan een nieuwe uitdaging begonnen als medisch project manager/medisch schrijver bij Ariez B.V.

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Chapter 11