Exercise therapy in people with rheumatoid arthritis and severe functional disability

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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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