Royal Dutch Society for Physical Therapy

the exercise therapist
CESAR-MENSENDIECK

VvOCM
Vereniging van Oefentherapeuten Cesar en Mensendieck

Justification

KNGF guideline

Rheumatoid arthritis

KNGF guideline Rheumatoid arthritis

Justification

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The KNGF aims to create the conditions in which high-quality physiotherapeutic care can be provided that is accessible to the entire Dutch population, whilst recognising the professional expertise of the physical therapist. The KNGF represents the professional, social and economic interests of over 19,000 registered physical therapists.

All sections of the guideline, including the summary, are available via www.kngf.nl/kennisplatform

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Justification for the Rheumatoid arthritis guideline

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Development of the guideline

Development of the Rheumatoid arthritis guideline

The Royal Dutch Society for Physical Therapy (KNGF) develops guidelines in accordance with its 'KNGF guideline methodology'.[1] This methodology meets the requirements – among others – as formulated by the Healthcare Institute of the Netherlands in the document 'Evaluation framework on the state of science and practice' [2] and the 'Guideline for guidelines' by the Management Board for Quality of Care.[3] The experts involved (Leiden University Medical Centre (LUMC) and KNGF) evaluate on a yearly basis whether the contextual and/or policy developments necessitate a revision of the guideline. If this is the case, revision takes place.

The revision of the 2008 KNGF guideline Rheumatoid arthritis started in 2016.[4] To this end, the authors of the guideline Rheumatoid arthritis and an independent chairman agreed to offer guidance to a guideline panel and a review panel, which had been duly appointed for this. The guideline panel held four meetings about the revision, the review panel met once and the guideline panel and review panel submitted input via email on three occasions. The entire guideline revision was completed in accordance with the KNGF guideline methodology.[1] All the guideline panel and review panel members signed the Declaration of interests form. This form was developed by the KNGF in the context of the guideline revision and is based on the 'Code for the prevention of undue influence as a result of a conflict of interests' by the Royal Dutch Academy of Sciences (KNAW).[5] All of the members of the guideline panel and the review panel represented a professional group or organisation that is relevant to this guideline revision.

Definition of the target group

This guideline is intended for physical therapists who treat patients with health problems resulting from RA in a monodisciplinary or multidisciplinary setting.

Definition of the health problem

This KNGF guideline describes the physiotherapeutic diagnostic process, therapeutic process and evaluation of patients who have been diagnosed with rheumatoid arthritis (RA) by the rheumatologist. The guideline is intended for treating patients with a nod for assistance that is related to RA, including the group of patients with RA who have joint replacement prostheses. In addition to complaints of the musculoskeletal system, people with RA can also have other acute and/or chronic conditions (comorbidity) or an increased risk of comorbidity. The relevant (risks of) comorbidity is described in the guideline. In addition, the guideline describes how to deal with comorbidity during the diagnostic and therapeutic process and evaluation.

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III Nynke Swart, MSc, physical therapist, physical therapy scientist, Quality Department employee, KNGF, Amersfoort.

IV Guus Meerhoff, MSc, physical therapist, human movement scientist, Quality Department senior employee, KNGF, Amersfoort.

V Thea Vliet Vlieland PhD, physical therapist, physician, epidemiologist, professor Effectiveness of Rehabilitation Processes and physical therapy in particular, Department of Orthopaedics, Rehabilitation &Physical Therapy and Department of Rheumatology at the Leiden University Medical Centre, Leiden.

Reading guide
This justification describes how the recommendations were determined – or the description per topic – during the guideline development process, including the literature that supports these recommendations or descriptions.
The recommendation or description per topic is the answer to the previously posed clinical questions. The clinical questions were drawn up based on an analysis of the barriers regarding physical therapy care of patients with RA. The barriers were identified using focus groups comprised of patients and physical therapists and by the guideline panel and the review panel.
The clinical questions were answered by describing the scientific literature (e.g. the clinical questions about the pathophysiology, clinical presentation and progression), or (if possible) with a systematic review according to the system of the Grading of Recommendations Assessment, Development and Evaluation working group (GRADE).[6]

For the clinical questions that were answered with a systematic review, this justification includes a description of all the steps that were undertaken pursuant to the GRADE system: formulation of the research question, design and execution of the search strategy, literature selection, description of the included studies, assessment of the effectiveness, quality of the evidence and determination of the remaining considerations (including the patient's values and preferences, costs, cost effectiveness and applicability in practice).

The GRADE assessment of the effectiveness and quality of evidence in the RA guideline
The following criteria were used to assess the magnitude of the effect: An SMD < 0.3 is considered to be a small effect of the intervention, 0.3–0.5 a moderate effect and > 0.5 a large effect. To assess the quality of the body of evidence, the quality of evidence per outcome measure was determined. The GRADE system has four levels of quality of evidence: 'high', 'moderate', 'low' or 'very low'. The starting point of the quality of evidence was high because only randomised controlled studies are included. Based on various factors, it may be necessary to adjust the quality of evidence downward. The GRADE system also uses criteria to adjust the quality of evidence upward; however, this was not the case for this guideline. Below is a description of the factors and considerations for down-grading:

- *Limitations in the study design and execution*. Limitations in study design and execution were low in the case of randomisation + allocation concealment + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading only took place for the high score.
- *Inconsistency of the results of the various studies*. Down-grading took place in the event of contradictory effects (I^2 > 40%).
- *Indirectness of evidence*. Down-grading took place if intermediate or surrogate outcome measures were used or if no head-to-head comparison of the experimental and standard intervention was available.
- *Imprecision of the estimated effect*. For dichotomous outcome measures, down-grading took place with a population of n < 300 and for continuous outcome measures down-grading took place with a population of n < 400.
- *Publication bias*. Down-grading took place if it was likely that studies with negative results were not submitted for publication.

Formulation of the recommendation
The formulation (direction and strength) of the recommendation was determined based on the results of the scientific literature and on additional considerations.

Type of recommendation	Formulation
Strong recommendation against the intervention	Do not offer the intervention
Conditional recommendation against the intervention	Consider not offering the intervention
Conditional recommendation against the intervention	Consider offering the intervention
Strong recommendation against the intervention	Offer the intervention

Sources

1. Meerhoff GA, Heijblom K, Knoop J. KNGF-richtlijnenmethodiek 2016 [KNGF guideline methodology 2016]. Methodology for development/revision and implementation of KNGF guidelines. Available at: https://www.kngf.nl/binaries/content/assets/kngf/onbeveiligd/vakgebied/kwaliteit/richtlijnen/kngf-richtlijnenmethodiek11-2017.pdf.
2. Zorginstituut Nederland [Healthcare Institute of the Netherlands] Beoordeling stand van de wetenschap en praktijk [Evaluation of the state of science and practice]. The Hague: Ministry of Health, Welfare and Sport; 2015. Available at: https://www.zorginstituutnederland.nl/publicaties/rapport/2015/01/15/beoordeling-stand-van-de-wetenschap-en-praktijk.
3. Regieraad Kwaliteit van Zorg [Management Board for Quality of Care]. Richtlijn voor Richtlijnen [Guideline for Guidelines]. The Hague: Regieraad Kwaliteit van Zorg [Management Board for Quality of Care]; 2012. Available at: http://www.haring.nl/download/literatuur/Richtlijn_voor_Richtlijnen_derde_herziene_versie.pdf.
4. Hurkmans EJ, van der Giesen FJ, Bloo H, et al. KNGF-richtlijn Reumatoïde artritis [KNGF guideline Rheumatoid arthritis]. Amersfoort: KNGF; 2008.
5. Code ter voorkoming van oneigenlijke beïnvloeding door belangenverstrengeling [Code for the prevention of undue influence as a result of a conflict of interests]. Utrecht: Koninklijke Nederlandse Akademie van Wetenschappen (KNAW) [Royal Netherlands Academy of Sciences]; 2012.
6. Grading of Recommendations Assessment, Development and Evaluation working group. Available at http://www.gradeworkinggroup.org/. Accessed 11 June 2018.

Note 1. Background

Clinical question

What is the pathophysiology of RA, what are the risk factors for the occurrence of RA, how often does RA occur in the Netherlands and what are the costs to society resulting from RA?

Sources

The following literature was used to answer the clinical question:

Pathophysiology and risk factors for disease development

1. Bijlsma JWJ, van Laar JM. Leerboek reumatologie en klinische immunologie [Textbook of rheumatology and clinical immunology]. Houten: Bohn Stafleu van Loghum; 2013.
2. Firestein GS, Budd RC, Gabriel SE, McInnes LB, O'Dell JR. Textbook of rheumatology. Part II. 10th edition. Philadelphia (USA): Elsevier; 2017.
3. van der Helm-van Mil AHM. Genetics, auto antibodies and clinical features in understanding and predicting rheumatoid arthritis. Leiden: Leiden University Medical Center; 2006.
4. van Gaalen F, Ioan-Facsinay A, Huizinga TW, Toes RE. The devil in the details: the emerging role of anticitrulline autoimmunity in rheumatoid arthritis. J Immunol. 2005;175:5575-80.
5. Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum. 2004;50:380-6.
6. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24.
7. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569-81.

Epidemiological data

1. Chronic rheumatic conditions. Available at http://www.who.int/chp/topics/rheumatic/en/. Accessed 11 June 2018.
2. Walker JM, Helewa A. Physical rehabilitation in arthritis. USA Edition. St. Louis: W.B. Saunders Company; 2004.
3. Reumatoïde artritis. Cijfers en context, huidige situatie. [Rheumatoid arthritis. Figures and context of current situation]. Available at: https://www.volksgezondheidenzorg.info/onderwerp/reumato%C3%AFde-artritis-ra/cijfers-context/huidige-situatie. Accessed 11 June 2018.
4. The healthcare and treatment data by Dutch hospitals provided by the DBC information system DIS of the Nederlandse Zorgautoriteit (NZa) [Dutch Healthcare Authority]. Available at: http://www.opendisdata.nl. Accessed 11 June 2018.

Consequences of RA and costs to society

1. Bijlsma JWJ, van Laar JM. Leerboek reumatologie en klinische immunologie [Textbook of rheumatology and clinical immunology]. Houten: Bohn Stafleu van Loghum; 2013.
2. Ranking of disorders based on burden of disease (in DALYs). Available at https://www.volksgezondheidenzorg.info/ranglijst/ranglijst-aandoeningen-op-basis-van-ziektelast-dalys. Accessed 21 May 2018.
3. Verstappen SM, Boonen A, Bijlsma JWJ, Buskens E, Verkleij H, et al. Working Status among Dutch patients with rheumatoid arthritis: work disability and working conditions. Rheumatology 2005;44:202-6.
4. NVR-NVVG Guideline on RA and participation in work 2015. Available at https://www.nvr.nl/wp-content/uploads/2014/11/NVR-NVVG-Richtlijn-RA-en-participatie-in-arbeid-2015.pdf.
5. Sloot R, Flinterman L, Heins M, Lafeber M, Boeije H, Poos R, et al. Rapport reumatische aandoeningen in Nederland [Report on rheumatic disorders in the Netherlands]. Utrecht: NIVEL; 2016. Available at https://reumanederland.nl/over-ons/over-reumanederland/publicaties/. Accessed 15 June 2018.
6. van den Akker-van Marle ME, Chorus AM, Vliet Vlieland TP, van den Hout WB. Cost of rheumatic disorders in the Netherlands. Best Pract Res Clin Rheumatol. 2012 Oct;26(5):721-31.
7. Chorus AMJ, Schokker DF. TNO report: Nationale Peiling Bewegingsapparaat [National Survey of the Musculoskeletal System] 2010, Leiden: TNO; 2011,
8. Costs of healthcare for rheumatoid arthritis according to age and gender. Available at https://www.volksgezondheidenzorg.info/onderwerp/reumato%C3%AFde-artritis-ra/kosten/kosten#node-kosten-van-zorg-voor-reumatoïde-artritis. Consulted on 11 June 2018.

Note 2. Clinical presentation, diagnosis, medical treatment and disease progression

Clinical question

What is the general clinical presentation of RA, how is the RA diagnosis made, what is the medical treatment and disease progression of RA?

Sources

The following literature was used to answer the clinical question:

Clinical presentation and disease progression

1. Walker JM, Helewa A. Physical rehabilitation in arthritis. USA Edition. St. Louis: W.B. Saunders Company; 2004.
2. Bijlsma JWJ, van Laar JM. Leerboek Reumatologie en klinische immunologie [Textbook of rheumatology and clinical immunology]. Houten: Bohn Stafleu van Loghum; 2013.
3. Firestein GS, Budd RC, Gabriel SE, McInnes LB, O'Dell JR. Textbook of rheumatology. Part II. 10th edition. Philadelphia (USA): Elsevier; 2017.
4. van der Helm-van Mil AHM. Genetics, auto antibodies and clinical features in understanding and predicting rheumatoid arthritis. Leiden: Leiden University Medical Center; 2006.
5. Ekdahl C, Broman G. Muscle strength, endurance, and aerobic capacity in rheumatoid arthritis: a comparative study with healthy subjects. Ann Rheum Dis. 1992;51(1):35-40.
6. Khurana R, Berney SM. Clinical aspects of rheumatoid arthritis. Pathophysiology. 2005;12(3):153-65.
7. Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). Ann Rheum Dis. 2014 Yesn;73(1):62-8.
8. Baillet A, Gossec L, Carmona L, Wit Md, van Eijk-Hustings Y, Bertheussen H, et al. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. Ann Rheum Dis. 2016 Jun;75(6):965-73.
9. Singh Yes, Cameron C, Noorbaloochi S, Cullis T, Tucker M, Christensen R, Ghogomu ET, Coyle D, Clifford T, Tugwell P, Wells GA. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet. 2015 Jul 18;386(9990):258-65.
10. Turesson C. Comorbidity in rheumatoid arthritis. Swiss Med Wkly. 2016 Apr 5;146:w14290.
11. Smulders YM, Burgers JS, Scheltens T, van Hout BA, Wiersma T, Simoons ML. Guideline development group for the Dutch guideline for multidisciplinary cardiovascular risk management. Clinical practice guideline for cardiovascular risk management in the Netherlands. Neth J Med. 2008 Apr;66(4):169-74.
12. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis. 2017 Yesn;76(1):17-28.
13. Dadoun S, Zeboulon-Ktorza N, Combescure C, Elhai M, Rozenberg S, Gossec L, et al. Mortality in rheumatoid arthritis over the last fifty years: systematic review and meta-analysis. Joint Bone Spine. 2013;80:29-33.
14. van den Hoek J, Roorda LD, Boshuizen HC, Tijhuis GJ, Dekker J, van den Bos GAM, et al. Trend in and predictors for cardiovascular mortality in patients with rheumatoid arthritis over a period of 15 years: a prospective cohort study. Clin Exp Rheum. 2016;34:813-9.

Diagnosis

1. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569–81.
2. NVR/CBO guideline 'Diagnostiek en behandeling van Reumatoïde Artritis' ['Diagnosis and treatment of rheumatoid arthritis']. Utrecht: Nederlandse Vereniging voor Reumatologie/Nederlands Huisartsengenootschap [Dutch Society for Rheumatology/Dutch College of General Practitioners]; 2009.
3. NHG Arthritis guideline panel. NHG Arthritis standard. Utrecht: Nederlands Huisartsengenootschap [Dutch College of General Practitioners]; 2017. Available at https://www.nhg.org/standaarden/volledig/nhg-standaard-artritis. Accessed 4 October 2018.
4. Combe B, Landewe R, Daien CI, Hua C, Aletaha D, Álvaro-Gracia JM, et al. 2016 update of the EULAR recommendations for the management of early arthritis. Ann Rheum Dis. 2016 Dec 15.

Medical treatment

1. Guidelines on medication: methotrexate. Update 2011. Utrecht: Nederlandse Vereniging voor Reumatologie [Dutch Society for Rheumatology]; 2011 Available at https://www.nvr.nl/wp-content/uploads/2014/11/NVR-Medicijnen-MTX-richtlijn-2009-update-2011.pdf.
2. Guideline on targeted use of biologicals for rheumatoid arthritis, axial spondyloarthritis and psoriatic arthritis. 2014 update. Utrecht: Nederlandse Vereniging voor Reumatologie [Dutch Society for Rheumatology]; 2014. Available at https://www.nvr.nl/wp-content/uploads/2014/11/NVR-Medicijnen-Update_Biologicals_richtlijn-23-6-2014.pdf.
3. Chatzidionysiou K, Emamikia S, Nam J, Ramiro S, Smolen J, van der Heijde D, et al. Efficacy of glucocorticoids, conventional and targeted synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2017 Jun;76(6):1102-1107.
4. Guideline on Diagnosing Rheumatoid Arthritis. Utrecht: Nederlandse Vereniging voor Reumatologie [Dutch Society for Rheumatology]; 2015. https://www.nvr.nl/wp-content/uploads/2016/10/Richtlijndiagnostiekreumatoafdeartritis_FINAL-def.pdf.
5. Combe B, Landewe R, Daien CI, Hua C, Aletaha D, Álvaro-Gracia JM, et al. 2016 update of the EULAR recommendations for the management of early arthritis. Ann Rheum Dis. 2016 Dec 15.

Disease progression

1. Guidelines on medication: methotrexate. Update 2011. Utrecht: Nederlandse Vereniging voor Reumatologie [Dutch Society for Rheumatology]; 2011 Available at https://www.nvr.nl/wp-content/uploads/2014/11/NVR-Medicijnen-MTX-richtlijn-2009-update-2011.pdf
2. Chatzidionysiou K, Emamikia S, Nam J, Ramiro S, Smolen J, van der Heijde D, et al. Efficacy of glucocorticoids, conventional and targeted synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2017 Jun;76(6):1102-1107.

Note 3. Prognostic factors for progression

Clinical question

Which prognostic factors play a role in the progression of the physical functioning of RA?

Sources

The following literature was used to answer the clinical question:

1. Albrecht K, Zink A. Poor prognostic factors guiding treatment decisions in rheumatoid arthritis patients: a review of data from randomized clinical trials and cohort studies. Arthritis Res Ther. 2017 Mar 23;19(1):68.
2. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis. 2017 Yesn;76(1):17-28.

Note 4. The care and role of the therapist

Clinical question

Which treatment options and organisation of care are recommended for people with RA and what is the role of the physical therapist or exercise therapist in treating patients with RA?

Sources

The following literature was used to answer the clinical question:

RA care

1. Multidisciplinary guideline on RA by the Nederlandse Vereniging voor Reumatologie (NVR) [Dutch Society for Rheumatology] In development.
2. Zangi HA, Ndosi M, Adams J, Andersen L, Bode C, Boström C, et al. EULAR recommendations for patient education for people with inflammatory arthritis. Ann Rheum Dis. 2015 Jun;74(6):954-62.
3. Concept consensus document Taakherschikking Reumatologie [Shifting of Tasks in Rheumatology]. Available at http://www.nhpr.nl/wp-content/uploads/2016/12/Aanbevelingen-RA-voet-Hoofddocument-maart-2017.pdf.
4. Daien CI, Hua C, Combe B, Landewe R. Non-pharmacological and pharmacological interventions

in patients with early arthritis: a systematic literature review informing the 2016 update of EULAR recommendations for the management of early arthritis. RMD Open. 2017 Yesn 5;3(1):e000404.
5. Kim SJ, Chen Z, Essani AB, Elshabrawy HA, Volin MV, Fantuzzi G, et al. Differential impact of obesity on the pathogenesis of RA or preclinical models is contingent on the disease status. Ann Rheum Dis. 2017 Apr;76(4):731-9.

Note 5. History taking

Clinical question

Which ICF domains are recommended to be quantified during the diagnostic process?

Sources

The following literature was used to answer the clinical question:

1. Kirchberger I, Glaessel A, Stucki G, Cieza A. Validation of the comprehensive international classification of functioning, disability and health core set for rheumatoid arthritis: the perspective of physical therapists. Phys Ther. 2007 Apr;87(4):368-84.

Note 6. Physical examination

Clinical question

What is the advice on which ICF domains should be quantified during the diagnostic process?

Sources

The following literature was used to answer the clinical question:

1. Kirchberger I, Glaessel A, Stucki G, Cieza A. Validation of the comprehensive international classification of functioning, disability and health core set for rheumatoid arthritis: the perspective of physical therapists. Phys Ther. 2007 Apr;87(4):368-84.
2. Munneke M, Verhoef J. Paramedische zorg bij reumatische aandoeningen [Paramedical care for rheumatic disorders]. Houten: Bohn Stafleu van Loghum, Springer Media BV; 2003.
3. Bijlsma JWJ, van Laar JM. Leerboek reumatologie en klinische immunologie [Textbook of rheumatology and clinical immunology]. Houten: Bohn Stafleu van Loghum; 2013.
4. Firestein GS, Budd RC, Gabriel SE, McInnes LB, O'Dell JR. Textbook of rheumatology. Part II, 10th edition. Philadelphia (USA): Elsevier; 2017. p 1167-86.
5. van der Leeden M, Steultjens M, Dekker JH, Prins AP, Dekker J. The relationship of disease duration to foot function, pain and disability in rheumatoid arthritis patients with foot complaints. Clin Exp Rheum. 2007;25(2):275-80,
6. van der Leeden M, Steultjens MP, Ursum J, Dahmen R, Roorda LD, Schaardenburg DV, et al. Prevalence and course of forefoot impairments and walking disability in the first eight years of rheumatoid arthritis. Arthritis Rheum. 2008;59(11):1596-602.
7. Rowbotham EL, Freeston JE, Emery P, Grainger AJ. The prevalence of tenosynovitis of the interosseous tendons of the hand in patients with rheumatoid arthritis. Eur Radiol. 2016 Feb;26(2):444-50,
8. Navarro-Compán V, Landewé R, Provan SA, Ødegård S, Uhlig T, Kvien TK, et al. Relationship between types of radiographic damage and disability in patients with rheumatoid arthritis in the EURIDISS cohort: a longitudinal study. Rheumatology (Oxford). 2015 Yesn;54(1):83-90.

Note 7. Measurement instruments

Clinical question

Which measurement instruments are recommended during the diagnostic phase and the evaluation of patients with RA?

Search strategy

A search for measurement instruments was performed on the website http://www.meetinstrumentenzorg.nl/ for all relevant outcome measures within the diagnostic process for treating patients with RA.
After the relevant measurement instruments were selected, an assessment was done to determine which parts of the ICF would be analysed with these measurement instruments. These were then divided, based on relevance, into recommended measurement instruments and optional measurement instruments. All measure-

ment instruments included in this guideline meet the criteria as described in the 'Measurement instruments framework for evidence-based products' of the KNGF.[1]

Sources

1. Swinkels RAHM, Meerhoff GA, Beekman E, Beurskens AJHM. Raamwerk Klinimetrie voor evidence based producten [Measurement instruments framework for evidence-based products]. Amersfoort: KNGF; 2016.
2. Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. Eur J Pain. 2004;8(4):283-91.
3. Jongert T, Benedictus J, Dijkgraaf J, Koers H, Oudhof J. Het gebruik van de Borgschaal bij bewegingsactiviteiten voor hartpatiënten [Use of the Borg scale for physical activities for heart patients]. Maarssen: Elsevier gezondheidszorg [Elsevier healthcare]; 2004.
4. Borg GA. Psychophysical bases of perceived exertion Med Sci Sports Exerc. 1982;14(5):377-81,
5. Bijlsma J, Oude Heuvel CHB, Zaalberg A. Development and validation of the Dutch questionnaire capacities of daily life (VDF) for patients with rheumatoid arthritis. J Rehab Sci. 1990; 3(3):71-4.
6. Oude Voshaar MA, ten Klooster PM, Taal E, van de Laar MA. Measurement properties of physical function scales validated for use in patients with rheumatoid arthritis: a systematic review of the literature. Health Qual Life Outcomes. 2011 Nov 7;9:99.
7. Beurskens AJHM. A patient-specific approach for measuring functional status in low back pain. Low back pain and traction. Thesis. Maastricht: Rijksuniversiteit Limburg [State University of Limburg]; 1996.
8. Kosak M, Smith T. Comparison of the 2-, 6-, and 12-minute walk tests in patients with stroke. J Rehabil Res Develop. 2005 Yesn-Feb;42(1):103-7.
9. Steffen TM, Hacker TA, Mollinger L. Age- and gender-related test performance in community-dwelling elderly people: Six-Minute Walk Test, Berg Balance Scale, Timed Up & Go Test, and gait speeds. Phys Ther. 2002;82(2):128-37.
10. Jones CJ, Rikli RE. Measuring functional fitness of older adults. J Act Aging. 2002;March-April:24-30,
11. Kim JK, Park MG, Shin SJ. What is the minimum clinically important difference in grip strength? Clin Orthop Relat Res. 2014 Aug;472(8):2536-41,
12. Morree JJ, Jongert MWA, van der Poel G. Inspanningsfysiologie, oefentherapie en training [Exercise physiology, exercise therapy and training]. Houten: Bohn Stafleu van Loghum; 2006.
13. McCurdy K, Langford G, Jenkerson D, Doscher M. The validity and reliability of the 1RM bench press using chainloaded resistance. J Strength Cond Res. 2008;22(3):678-83.
14. Verdijk LB, van Loon L, Meijer K, Savelberg HH. One-repetition maximum strength test represents a valid means to assess leg strength in vivo in humans. J Sports Sci. 2009;27(1):59-68.
15. Beaton DE, Wright JG, Katz JN, Upper extremity collaborative group. Development of the QuickDASH: comparison of three item-reduction approaches. J Bone Joint Sur (Am). 2005 May;87(5):1038-46.
16. Kennedy CA, Beaton DE, Smith P, van Eerd D, Tang K, Inrig T, et al. Measurement properties of the QuickDASH (Disabilities of the Arm, Shoulder and Hand) outcome measure and cross-cultural adaptations of the QuickDASH: a systematic review. Qual Life Res. 2013 Nov;22(9):2509-47.
17. Ainsworth BE, Haskell WL, Herrmann SD, et al. The compendium of physical activities tracking guide. Tempe: Arizona State University; 2011. Available at http://prevention.sph.sc.edu/tools/docs/documents_compendium.pdf
18. Achttien RJ, Staal JB, Merry AHH, van der Voort SSEM, Klaver RJ, Schoonewille S, et al. KNGF-richtlijn Hartrevalidatie: bijlage II [KNGF guideline Cardiac rehabilitation: Appendix II]. Amersfoort: Koninklijk Nederlands Genootschap voor Fysiotherapie (KNGF) [Royal Dutch Society for Physical Therapy]; 2005
19. Zhang W, Bansback N, Boonen A, Young A, Singh A, Anis A. Validity of the work productivity and activity impairment questionnaire - general health version in patients with rheumatoid arthritis. Arthritis Res Ther. 2010;12(5):R177.
20. Lee J, Kim SH, Moon SH, Lee EH. Measurement properties of rheumatoid arthritis-specific quality-of-life questionnaires: systematic review of the literature. Qual Life Res. 2014. Dec;23(10)2779-91,
21. van Poppel MN. International Physical Activity Questionnaire. Amsterdam: EMGO-instituut [EMGO Institute].
22. Forsén L, Loland NW, Vuillemin A, Chinapaw MJ, van Poppel MN, Mokkink LB, et al. Self-administered physical activity questionnaires for the elderly: a systematic review of measurement properties. Sports Med. 2010 Jul 1;40(7):601-23.
23. Exercise guidelines 2017. Summary. The Hague: Gezondheidsraad [Dutch Health Council]; 2017. Available at https://www.gezondheidsraad.nl/sites/default/files/grpublication/samenvatting_beweegrichtlijnen_2017_1.pdf.

24. Ostelo RWJG, Deyo RA, Stratford P, Waddell G, Croft P, von Korff M, et al. Interpreting change scores for pain and functional status in low back pain towards international consensus regarding minimal important change. Spine; 2008 Yesn 1;33(1):90-4.
25. Yescobsen F, Holten O, Faugli H, Leirvik R. Medical exercise therapy. Man Ther Norway. 1992;7:19-22.

Note 8. Determination of indications and contraindications for exercise therapy, and red and yellow flags

Clinical question

What is the indication for physical or exercise therapy for people with RA and based on which criteria and/or red flags should people with RA be referred back to the GP or treating specialist?

Sources

The following literature was used to answer the clinical question:

1. NHG Arthritis guideline panel. NHG Arthritis standard. Utrecht: Nederlands Huisartsengenootschap [Dutch College of General Practitioners]; 2017. Available at https://www.nhg.org/standaarden/volledig/nhg-standaard-artritis. Accessed 4 October 2018.
2. Hurkmans EJ, van der Giesen FJ, Bloo H, Boonman DC, van der Esch M, Fluit M, et al. KNGF-richtlijn Reumatoïde artritis [KNGF guideline Rheumatoid arthritis]. Update regarding measurement instruments 2017. Amersfoort: KNGF; 2008.
3. Eumusc.net: Driving musculoskeletal health for Europe. Standard of Care for People with Rheumatoid Arthritis. Available at http://www.eumusc.net/workpackages_wp5.cfm.
4. EUMUS.net. Standards of care for people with rheumatoid arthritis. Available at http://www.eumusc.net/myUploadData/files/RA_Full_draft_FINAL_V21.pdf.
5. CBO guideline Rheumatoid Arthritis Available at https://www.nvr.nl/wp-content/uploads/2014/11/CBO-richtlijn-reumatode-artritis-2009.pdf.
6. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2007 Yesn;66(1):34-45.
7. Deighton C, O'Mahony R, Tosh J, Turner C, Rudolf M. Guideline Development Group. Management of rheumatoid arthritis: summary of NICE guidance. BMJ. 2009 Mar 16;338:b702.
8. Briggs AM, Fary RE, Slater H, Ranelli S, Chan M. Physiotherapy co-management of rheumatoid arthritis: identification of red flags, significance to clinical practice and management pathways. Man Ther. 2013 Dec;18(6):583-7.
9. Slater H, Briggs AM, Fary RE, Chan M. Upper cervical instability associated with rheumatoid arthritis: what to 'know' and what to 'do'. Man Ther. 2013 Dec;18(6):615-9.

Note 9. Information and advice

Clinical question

What are the recommendations for providing information and advice for patients with RA?

Complete clinical question according to PICO

Is information and advice (I), either with or without the exercise therapy intervention, recommended for patients with RA (P) for facilitating effective self-management and a healthy lifestyle (O)?

Search strategy

On March 3, 2017, the KNGF conducted a search on studies that describe which information and advice physical therapists should offer patients with RA in order to facilitate self-management.

Literature found

A total of 755 references were found. Ultimately, one international EULAR guideline was selected to answer the clinical question.[1]

Description of studies

The evidence up to and including 2015 is summarised in the EULAR guideline.[1] A total of 115 studies are included in this guideline, consisting of 11 systematic reviews or meta-analyses, 36 randomised studies (reported in 44 studies), seven controlled studies, nine pre-post-test studies, 23 cross-sectional studies and 21

qualitative studies. Based on these studies, two overarching principles and eight specific recommendations regarding information and advice in patients with inflammatory rheumatic disorders were formulated. The EULAR guideline is based on literature about various types of programmes: educational programmes (32 studies), self-management programmes (7 studies), cognitive behaviour therapy (9 studies) and stress management programmes (6 studies). In addition three systematic reviews about these various information and advice programmes were included.

Effectiveness and quality of the body of evidence
Multiple systematic reviews included in the EULAR guideline showed that in particular programmes that are based on a theoretical framework (especially self-management programmes, cognitive behaviour therapy and stress management programmes) have a small but positive effect on the self-reported degree of physical activity, pain, limitations in activities, symptoms of depression, anxiety and fatigue (4-18 month follow-up). The EULAR guideline had an acceptable quality according to AGREE 2.0 (5 of 7 points).

From evidence to recommendation
The guideline panel formulated a recommendation for daily practice based on the EULAR guideline.

Sources
1. Zangi HA, Ndosi M, Adams J, Anderson L, Bode C, et al. EULAR recommendations for patient education for people with inflammatory arthritis. Ann Rheum Dis. 2015;74;6:1-9.

Note 10. Exercise therapy

Clinical question
Is exercise therapy recommended for patients with RA?

Complete clinical question according to PICO
Are exercise therapy interventions (I), compared to no exercise therapy (C), recommended for the treatment of patients with RA (P) to improve their quality of life, physical functioning, pain, fatigue, aerobic capacity, muscle strength, range of motion and work productivity (O)? Undesirable effects of exercise therapy interventions are also determined, defined as increased pain, increased disease activity and radiological damage.

Search strategy
On March 3, 2017, the KNGF conducted a search on a summary of the literature (i.e. systematic review) and randomised controlled studies on exercise therapy in patients with RA. The search terms for exercise therapy are included in the attachment to this Note. The selection criteria for inclusion are shown in table 10.1.

Table 10.1. Selection criteria for systematic review of exercise therapy.

Type of study	RCT's
Type of patient	adults diagnosed with rheumatoid arthritis in accordance with the ARA or ACR/ EULAR classification criteria
Type of intervention	Indication 1 Any form of exercise therapy (irrespective of frequency, intensity, type, duration and form) aimed at improving the aerobic capacity, muscle strength of one or more large muscle groups, range of motion of the large joints and/or balance training. In addition, the exercise programme should be unsupervised at least 50% of the time. Indication 2 Any form of fully supervised exercise therapy (irrespective of frequency, intensity, type, duration and form) aimed at improving the aerobic capacity, muscle strength of one or more large muscle groups, range of motion of the large joints and/or balance training. Indication 3 Any form of fully supervised exercise therapy (irrespective of frequency, intensity, type, duration and form) aimed at improving the aerobic capacity, muscle strength of one or more large muscle groups, range of motion of the large joints and/or balance training for patients with serious disease progression (disease activity DAS28 > 5.3 and/or functional class III and IV, and/or comorbidity).

Type of comparison	no exercise therapy or 'usual care' (physical therapy in control group acceptable)
Type of outcome	crucial outcome measures: quality of life, physical functioning, pain*, fatigue important outcome measures: aerobic capacity, muscle strength, range of motion, disease activity*, radiological damage*, work productivity
Type of timeline	immediately after the intervention

** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.*

Literature found

The literature search yielded 1837 references. Based on the quality, the characteristics of the interventions included, the number of outcome measures included and whether GRADE was applied, a decision was made to take the Cochrane review by Hurkmans et al.[1] as the starting point for answering this clinical question. This systematic literature review includes literature up to December 2008 and scores high on AMSTAR (9 out of 11 points). The KNGF complemented the systematic review by Hurkmans et al. by including randomised controlled studies up to 3 March 2017. In addition, the randomised controlled studies that were excluded by Hurkmans et al. due to low intensity or minimal supervision, were included for this clinical question. The literature was divided into exercise therapy for indication 1, 'studies in which the exercise programme was not supervised at least 50% of the time', indication 2 'fully supervised exercise therapy' and indication 3 'fully supervised exercise therapy for patients with serious disease progression and/or comorbidity'. Ultimately, four randomised controlled studies met the selection criteria for indication 1 [2-5] and 19 randomised controlled studies met the selection criteria for indication 2 [6-24]. No studies were found for indication 3. The results of the reviews for indication 1, 2 and 3 can be found in Note 11, 12 and 13, respectively.

The flowcharts of one or more systematic reviews on exercise therapy for indication 1, 2 and 3, respectively, are included in the appendix to this Note.

Sources

1. Hurkmans E, van der Giesen FJ, Vliet Vlieland TP, Schoones J, Van den Ende EC. Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. Cochrane Database Syst Rev. 2009;7:4.
2. Durcan L, Wilson F, Cunnane G. The effect of exercise on sleep and fatigue in rheumatoid arthritis: a randomized controlled study. J Rheumatol. 2014 Oct;41(10):1966-73.
3. Häkkinen A, Sokka T, Kotaniemi A, Hannonen P. A randomized two-year study of the effects of dynamic strength training on muscle strength, disease activity, functional capacity, and bone mineral density in early rheumatoid arthritis. Arthritis Rheum. 2001 Mar;44(3):515-22.
4. Manning VL, Hurley MV, Scott DL, Coker B, Choy E, Bearne LM. Education, self-management, and upper extremity exercise training in people with rheumatoid arthritis: a randomized controlled trial. Arthritis Care Res (Hoboken). 2014 Feb;66(2):217-27.
5. Stenström CH, Arge B, Sundbom A. Home exercise and compliance in inflammatory rheumatic diseases, a prospective clinical trial. J Rheumatol. 1997;24:2.
6. Baillet A, Payraud E, Niderprim VA, Nissen MJ, Allenet B, François P, et al. A dynamic exercise programme to improve patients' disability in rheumatoid arthritis: a prospective randomized controlled trial. Rheumatology (Oxford). 2009 Apr;48(4):410-5.
7. Baslund B, Lyngberg K, Andersen V, Halkyeser Kristensen J, Hansen M, Klokker M, et al. Effect of 8 wk of bicycle training on the immune system of patients with rheumatoid arthritis. J Appl Physiol. 1993;75:1691-5.
8. Bearne LM, Scott DL, Hurley MV. Exercise can reverse quadriceps sensorimotor dysfunction that is associated with rheumatoid arthritis without exacerbating disease activity. Rheumatology (Oxford). 2002 Feb;41(2):157-66.
9. Bilberg A, Ahlmén M, Mannerkorpi K. Moderately intensive exercise in a temperate pool for patients with rheumatoid arthritis: a randomized controlled study. Rheumatology (Oxford). 2005 Apr;44(4):502-8.
10. Breedland I, van Scheppingen C, Leijsma M, Verheij-Yesnsen NP, van Weert E. Effects of a group-based exercise and educational program on physical performance and disease self-management in rheumatoid arthritis: a randomized controlled study. Phys Ther. 2011 Jun;91(6):879-93.
11. Da Silva KN, Teixeira LE, Imoto AM, Atallah AN, Peccin MS, Trevisani VF. Effectiveness of sensorimotor training in patients with rheumatoid arthritis: a randomized controlled trial. Rheumatol Int. 2013 Sep;33(9):2269-75.

12. de Jong Z, Munneke M, Zwinderman AH, Kroon HM, Yesnsen A, Ronday KH, et al. Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. Arthritis Rheum. 2003;48(9):2415-24.
13. Flint-Wagner HG, Lisse J, Lohman TG, Going SB, Guido T, Cussler E, Gates D, Yocum DE. Assessment of a sixteen-week training program on strength, pain, and function in rheumatoid arthritis patients. J Clin Rheumatol. 2009 Jun;15(4):165-71,
14. Häkkinen A, Häkkinen K, Hannonen P. Effects of strength training on neuromuscular function and disease activity in patients with recent-onset inflammatory arthritis. Scand J Rheumatol. 1994;23(5):237-42.
15. Hansen TM, Hansen G, Langgaard AM, Rasmussen JO. Longterm physical training in rheumatoid arthritis. A randomized trial with different training programs and blinded observers. Scand J Rheumatol. 1993;22(3):107-12.
16. Harkcom TM, Lampman RM, Banwell BF, Castor CW. Therapeutic value of graded aerobic exercise training in rheumatoid arthritis. Arthr Rheum. 1985;28(1):32-9.
17. Lemmey AB, Marcora SM, Chester K, Wilson S, Casanova F, Maddison PJ. Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial. Arthritis Rheum. 2009 Dec 15;61(12):1726-34.
18. Lyngberg KK, Harreby M, Bentzen H, Frost B. Elderly rheumatoid arthritis on steroid treatment tolerate physical training without an increase in disease activity. Arch Phys Med Rehab. 1994;75:1189-95.
19. McMeeken J, Stillman B, Story I, Kent P, Smith J. The effects of kno extensor and flexor muscle training on the timed-up-and-go test in individuals with rheumatoid arthritis. Physiother Res Int. 1999;4(1):55-67.
20. Minor MA, Hewett JE, Webel RR, Anderson SK, Kay DR. Efficacy of physical conditioning exercise in patients with rheumatoid arthritis and osteoarthritis. Arthritis Rheum. 1989;32(11):1396-405.
21. Sanford-Smith S, Mackay-Lyons M, Nunes-Clement S. Therapeutic benefit of aquaerobics for individuals with rheumatoid arthritis. Physiotherapy Canada 1998;Winter:40–6.
22. Siqueira US, Orsini Valente LG, de Mello MT, Szejnfeld VL, Pinheiro MM. Effectiveness of aquatic exercises in women with rheumatoid arthritis: a randomized, controlled, 16-week intervention – the HydRA Trial. Am J Phys Med Rehabil. 2017 Mar;96(3):167-75.
23. Strasser B, Leeb G, Strehblow C, Schobersberger W, Haber P, Cauza E. The effects of strength and endurance training in patients with rheumatoid arthritis. Clin Rheumatol. 2011 May;30(5):623-32.
24. van den Ende CHM, Hazes JMW, Le Cessie S, Mulder WJ, Belfor DG, Breedveld FC, et al. Comparison of high and low intensity training in well controlled rheumatoid arthritis. Results of a randomized clinical trial. Ann Rheum Dis. 1996;55(11):798-805.

Note 11. Exercise therapy for indication 1

Clinical question

Is exercise therapy recommended for patients with indication 1?

Complete clinical question according to PICO

To answer this clinical question, a joint PICO clinical question was formulated for indication 1, 2 and 3 (see Note 10).

Search strategy

A joint search was conducted for indication 1, 2 and 3 (see Note 10).

Literature found

Ultimately, four randomised controlled studies met the selection criteria for indication 1 [1-4]. Note 10 contains an explanation of how this literature was found.

Description of studies

The included patients (n = 282) were 54 years old on average and 68% were female. In three studies the intervention consisted of one-time instructions about how the participants could implement the exercise programme at home.[1-3] In the fourth study the intervention consisted of four times group instruction (education and exercises), after which the patients implemented the exercise programme independently at home. [4] In one study the control group received the usual care[4], and in three studies the control group received one-time advice about the added values of the exercises[1], stretching and range-of-motion exercises [2] and relaxation exercises[3], respectively.

Effectiveness and quality of evidence

The assessment of the study design and execution of the selected articles is included in the appendix to this Note. This is followed by a description of the effectiveness and the quality of evidence of exercise therapy for indication 1 for each outcome measure. See also the GRADE profile of exercise therapy for indication 1 in table 11.1.

Desired effects

Crucial outcome measures

a) 'Quality of life' outcome measure (2 studies):
   - There is a moderate effect (SMD = 0.44; 95%-CI = -0.34–1.22) of exercise therapy with limited supervision on the 'quality of life' outcome measure for patients with RA compared to no treatment with exercise therapy with limited supervision.
   - The quality of evidence for the 'quality of life' outcome measure was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and small number of patients (inaccuracy).

b) 'Physical functioning' outcome measure (3 studies):
   - There is a moderate effect (SMD = 0.32; 95%-CI = 0.02–0.62) of treatment with exercise therapy with limited supervision on the physical functioning of patients with RA compared to no treatment with exercise therapy with limited supervision.
   - The quality of evidence value for the 'physical functioning' outcome measure was lowered by two levels to 'low quality of evidence', given the limitations of the study design and execution and the small number of patients (inaccuracy).

c) 'Fatigue' outcome measure (1 study):
   - The effect of treatment with exercise therapy with limited supervision on fatigue in patients with RA compared to no treatment with exercise therapy with limited supervision is unknown (SMD unavailable).
   - The quality of evidence for the 'fatigue' outcome measure was lowered by two levels to 'low quality of evidence', given the limitations of the study design and execution and the small number of patients (inaccuracy).

d) 'Pain' outcome measure (4 studies):
   - There is a large effect (SMD = 0.54; 95%-CI = 0.22–0.87) of treatment with exercise therapy with limited supervision on pain in patients with RA compared to no treatment with exercise therapy with limited supervision.
   - The quality of evidence for the 'pain' outcome measure was lowered by three levels to 'very low quality of evidence', given the limitations of the study design and execution, the contradictory results (inconsistency) and the small number of patients (inaccuracy).

Important outcome measures

a) 'Aerobic capacity' outcome measure (no studies): the effectiveness and quality of evidence could not be determined.

b) 'Muscle strength' outcome measure (1 study):
   - There is a slight effect (SMD = 0.24; 95%-CI = -0.09–0.57) of treatment with exercise therapy with limited supervision on muscle strength in patients with RA compared to no treatment with exercise therapy with limited supervision.
   - The quality of evidence for the 'muscle strength' outcome measure was lowered by one level to 'acceptable quality of evidence', given the small number of patients (inaccuracy).

c) 'Range of motion' outcome measure (no studies): the effectiveness and quality of evidence could not be determined.

d) 'Work productivity' outcome measure (no studies): the effectiveness and quality of evidence could not be determined.

Undesirable effects

a) 'Disease activity' outcome measure (2 studies):
   - There is a slight effect (SMD = 0.60; 95%-CI = -0.56–1.77) in favour of treatment with exercise therapy with limited supervision on disease activity in patients with RA compared to no treatment with exercise therapy with limited supervision.
   - The quality of evidence for the 'disease activity' outcome measure was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and small number of patients (inaccuracy).

b) 'Radiological damage' outcome measure (2 studies):
- There is a moderate effect (SMD = 0.32; 95%-CI = -0.43-1.07) in favour of treatment with exercise therapy with limited supervision on radiological damage in patients with RA compared to no treatment with exercise therapy with limited supervision.
- The quality of evidence for the 'radiological damage' outcome measure was lowered by three levels to 'very low quality of evidence', given the limitations of the study design and execution, contradictory results (inconsistency) and small number of patients (inaccuracy).

Table 11.1 GRADE profile of exercise therapy for indication 1.

	Number of studies	GRADE+					Number of patients		Estimated effect	Quality of evidence
		Limitations in study design and execution[a]	Inconsistency[b]	Indirectness	Inaccuracy[c]	Other	Exercise therapy	Control	Standardized mean difference (95%-CI)[d]	very low / low / acceptable / high[e]
Desired effects	**Crucial outcome measures**									
	Quality of life									
	n = 2	moderate	yes, I^2 = 74%	no	yes, *n* = 142	no	69	73	0,44 (-0,34 to 1,22)	low (3)
	Physical functioning									
	n = 3	high	no, I^2 = 0%	no	yes, *n* = 174	no	88	86	0,32 (0,02 to 0,62)	low (5)
	Fatigue									
	n = 1	low	n/a	no	yes, *n* = 108	no	52	56	no significant effect compared to usual care	low (5)
	Pain									
	n = 4	high	yes, I^2 = 42%	no	yes, *n* = 282	no	140	142	0,54 (0,22 to 0,87)	very low (6)
	Important outcome measures									
	Aerobic capacity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Muscle strength									
	n = 2	moderate	no, I^2 = 0%	no	yes, *n* = 142	no	69	73	0,24 (-0,09 to 0,57)	acceptable (2)
	Range of motion									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Work productivity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Undesirable effects[f]	**Disease activity**									
	n = 2	moderate	yes, I^2 = 92%	no	yes, *n* = 170	no	83	87	0,60 (-0,56 to 1,77)	low (3)
	Radiological damage									
	n = 2	high	yes, I^2 = 69%	no	yes, *n* = 98	no	48	48	0,32 (-0,43 to 1,07)	very low (6)

n/a: not applicable. **a** Limitations in study design and execution were low in the case of random assignment + allocation concealed + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading took place with a high score. **b** Down-grading took place with I2 > 40%. **c** Down-grading took place in the event of a dichotomous outcome measure with n < 300 and in the case of a continuous outcome measure with *n* < 400. **d** A positive standardised mean difference (SMD) reflects a benefit for the intervention group compared to the control group. If one study measured the respective outcome measure, the results from this study are described. An SMD of < 0.3 is considered as a slight effect of the intervention; 0.3-0.5 as a moderate effect and > 0.5 as a large effect. **e** 1 = down-grading for inconsistency; 2 = down-grading for inaccuracy; 3 = down-grading for inconsistency and inaccuracy; 4 = down-grading for limitations in the study design and method and inconsistency; 5 = down-grading for limitations in study design and method and inaccuracy; 6 = down-grading for limitations in study design and method, inconsistency and inaccuracy. **f** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.

From evidence to recommendation

When formulating the recommendation (direction and strength) for exercise therapy for indication 1, the guideline panel additionally considered the following. See also the assessment form from evidence to recommendation for exercise therapy for indication 1 in the appendix to this Note.

- The desired effects (improvement of the quality of life, degree of physical activity and fatigue) of exercise therapy are present, while the undesirable effects (increased pain, disease activity and/or radiological damage) were in favour of the exercise therapy. Even though the estimated effects are of limited magnitude and there is uncertainty about the probability of the estimated effects, the guideline panel believes that the desired effects outweigh the undesirable effects.
- How much patients value hand exercises will likely differ from patient to patient. The guideline panel estimates that most patients will have a positive view of exercise therapy due to its favourable effects and because patients can easily incorporate this into their daily lives.
- The costs of exercise therapy for the patient depend on the current government regulations regarding medical expenses (see Rijksoverheid.nl) but in general remain limited because the physical therapist gives as little guidance as possible. There are few to no costs associated with exercise therapy for the physical therapist, based on the assumption that the required exercise equipment is already present.
- The cost-effectiveness of an exercise programme with limited supervision by a physical therapist has been demonstrated (ICER: € 3,122).[5] At a willingness-to-pay of £ 20,000 per QALY, the researchers arrived at a probability of 65% that exercise therapy with limited supervision is the most cost-effective option, with the quality of evidence being assessed pursuant to the CHEC list for economic evaluations with a score of 14 on a scale of 19 (with 19 being the highest quality).
- The guideline panel deems that implementing the intervention in daily practice is acceptable and feasible because the intervention is viewed as the most indicated treatment option and no specific resources are required.

Sources

1. Durcan L, Wilson F, Cunnane G. The effect of exercise on sleep and fatigue in rheumatoid arthritis: a randomized controlled study. J Rheumatol. 2014 Oct;41(10):1966-73.
2. Häkkinen A, Sokka T, Kotaniemi A, Hannonen P. A randomized two-year study of the effects of dynamic strength training on muscle strength, disease activity, functional capacity, and bone mineral density in early rheumatoid arthritis. Arthritis Rheum. 2001 Mar;44(3):515-22.
3. Manning VL, Hurley MV, Scott DL, Coker B, Choy E, Bearne LM. Education, self-management, and upper extremity exercise training in people with rheumatoid arthritis: a randomized controlled trial. Arthritis Care Res (Hoboken). 2014 Feb;66(2):217-27.
4. Stenström CH, Arge B, Sundbom A. Home exercise and compliance in inflammatory rheumatic diseases, a prospective clinical trial. J Rheumatol. 1997;24:2.
5. Manning VL, Kaambwa B, Ratcliffe J, Scott DL, Choy E, Hurley MV, Bearne LM. Economic evaluation of a brief education, self-management and upper limb exercise training in people with rheumatoid arthritis (EXTRA) programme: a trial-based analysis. Rheumatology (Oxford). 2015 Feb;54(2):302-9.

Note 12. Exercise therapy for indication 2

Clinical question

Is exercise therapy recommended for patients with indication 2?

Complete clinical question according to PICO

To answer this clinical question, a joint PICO clinical question was formulated for indication 1, 2 and 3 (see Note 10).

Search strategy

A joint search was conducted for indication 1, 2 and 3 (see Note 10).

Literature found

Ultimately, 19 randomised controlled studies met the selection criteria for indication 2.[1-19] Note 10 contains an explanation of how this literature was found.

Description of studies

The included patients (n = 1101) were 54 years old on average, and 70% were female. In 14 studies the patients had low disease activity on average and in five studies they had moderate disease activity. In the majority of

the included studies patients with comorbidity were excluded, with the exception of one study in which 16% of patients had hypertension. Patients with functional class III and IV were excluded in six studies. Patients with functional class III were included in one study. The functional class was not reported in the other 12 studies. In eight studies the intervention consisted of a combination of exercises for improving strength and endurance.[1,4,5,7,9,13,17–19] In five studies the exercise therapy was aimed at improving strength [3,8,12,14,19], and in five studies on improving endurance.[2,10,11,15,16] In one study the intervention was aimed at improving balance.[6] The intervention in the control group consisted of no intervention in 11 studies [2,6–11,13–15,17], (instructions for) homework exercises in three studies [4,12,18], a waiting list in two studies [3,5], range of motion exercises in two studies [16,19] and education in one study [1].

Effectiveness and quality of evidence
The assessment of the study design and execution of the selected articles is included in the appendix to this Note.

Below follows a description of the effectiveness of exercise therapy for indication 2 as well as the quality of evidence for each outcome measure. See also the GRADE profile of exercise therapy for indication 2 in table 12.1.

Desired effects

Crucial outcome measures

a) 'Quality of life' outcome measure (3 studies):
   - There is a large effect (SMD = 0.70; 95%-CI = 0.14–1.25) of treatment with supervised exercise therapy on quality of life compared to no treatment with supervised exercise therapy.
   - The quality of evidence for the 'quality of life' outcome measure was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and the small number of patients (inaccuracy).

b) 'Physical functioning' outcome measure (17 studies):
   - There is a moderate effect (SMD = 0.43; 95%-CI = 0.18–0.68) of treatment with supervised exercise therapy on physical functioning compared to no treatment with supervised exercise therapy.
   - The quality of evidence for the 'physical functioning' outcome measure was lowered by one level to 'moderate quality of evidence', given the contradictory results (inconsistency).

c) 'Fatigue' outcome measure (no studies): the effectiveness and quality of evidence could not be determined.

d) 'Pain' outcome measure (3 studies):
   - There is a moderate effect (SMD = 0.49; 95%-CI = 0.13–1.11) of treatment with supervised exercise therapy on pain compared to no treatment with supervised exercise therapy.
   - The quality of evidence for the 'pain' outcome measure was lowered by three levels to 'very low quality of evidence', given the limitations of the study design and execution, the contradictory results (inconsistency) and the small number of patients (inaccuracy).

Important outcome measures

a) 'Aerobic capacity' outcome measure (11 studies):
   - There is a moderate effect (SMD = 0.49; 95%-CI = 0.33–0.65) of treatment with supervised exercise therapy on aerobic capacity compared to no treatment with supervised exercise therapy.
   - The quality of evidence for the 'aerobic capacity' outcome measure was not lowered.

b) 'Muscle strength' outcome measure (12 studies):
   - There is a large effect (SMD = 0.63; 95%-CI = 0.21–1.05) of treatment with supervised exercise therapy on muscle strength compared to no treatment with supervised exercise therapy.
   - The quality of evidence for the 'muscle strength' outcome measure was lowered by two levels to 'low quality of evidence', given the limitations of the study design and execution and the contradictory results (inconsistency).

c) 'Range of motion' outcome measure (2 studies):
   - There is a large effect (SMD = 0.59; 95%-CI = 0.17–1.01) of treatment with supervised exercise therapy on range of motion compared to no treatment with supervised exercise therapy.
   - The quality of evidence for the 'range of motion' outcome measure was lowered by one level to 'moderate quality of evidence', given the small number of patients (inaccuracy).

d) 'Work productivity' outcome measure (0 studies): the effectiveness and quality of evidence could not be determined.

Undesirable effects

a) 'Disease activity' outcome measure (9 studies):
   - There is a large effect (SMD = 0.23; 95%-CI = 0.16-0.62) in favour of treatment with supervised exercise therapy on disease activity compared to no treatment with supervised exercise therapy.
   - The quality of evidence for the 'disease activity' outcome measure was lowered by one level to 'moderate quality of evidence', given the contradictory results (inconsistency).

b) 'Radiological damage' outcome measure (2 studies):
   - There is a slight effect (SMD = 0.09; 95%-CI = 0.14-0.31) in favour of treatment with supervised exercise therapy on radiological damage compared to no treatment with supervised exercise therapy.
   - The quality of evidence for the 'radiological damage' outcome measure was lowered by one level to 'moderate quality of evidence', given the small number of patients (inaccuracy).

Table 12.1 GRADE profile of exercise therapy for indication 2.

	Number of studies	GRADE+					Number of patients		Estimated effect	Quality of evidence
		Limitations in study design and execution[a]	Inconsistency[b]	Indirectness	Inaccuracy[c]	Other	Exercise therapy	Control	Standardized mean difference (95%-CI)[d]	very low / low / acceptable / high[e]
Desired effects	**Crucial outcome measures**									
	Quality of life									
	n = 3	low	yes, I^2 = 70%	no	yes, *n* = 193	no	96	97	0,70 (0,14 to 1,25)	low (3)
	Physical functioning									
	n = 17	moderate	no, I^2 = 67%	no	no, *n* = 988	no	499	489	0,43 (0,18 to 0,68)	moderate (1)
	Fatigue									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Pain									
	n = 3	high	yes, I^2 = 77%	no	yes, *n* = 219	no	114	105	0,49 (-0,13 to 1,11)	very low (6)
	Important outcome measures									
	Aerobic capacity									
	n = 11	moderate	no, I^2 = 0%	no	no, *n* = 626	no	314	312	0,49 (0,33 to 0,65)	high
	Muscle strength									
	n = 12	high	yes, I^2 = 83%	no	no, *n* = 695	no	341	354	0,63 (0,21 to 1,05)	low (4)
	Range of motion									
	n = 2	moderate	no, I^2 = 0%	no	yes, *n* = 93	no	45	48	0,59 (0,17 to 1,01)	moderate (2)
	Work productivity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Undesirable effects[f]	**Disease activity**									
	n = 7	moderate	yes, I^2 = 71%	no	no, *n* = 560	no	275	285	0,23 (-0,16 to 0,62)	moderate (1)
	Radiological damage									
	n = 2	moderate	no, I^2 = 0%	no	yes, *n* = 305	no	147	158	0,09 (-0,14 to 0,31)	moderate (1)

n/a: not applicable. **a** Limitations in study design and execution were low in the case of random assignment + allocation concealed + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading took place with a high score. **b** Down-grading took place with I2 > 40%. **c** Down-grading took place in the event of a dichotomous outcome measure with n < 300 and in the case of a continuous outcome measure with *n* < 400. **d** A positive standardised mean difference (SMD) reflects a benefit for the intervention group compared to the control group. If one study measured the respective outcome measure, the results from this study are described. An SMD of < 0.3 is considered as a slight effect of the intervention; 0.3-0.5 as a moderate effect and > 0.5 as a large effect. **e** 1 = down-grading for inconsistency; 2 = down-grading for inaccuracy; 3 = down-grading for inconsistency and inaccuracy; 4 = down-grading for limitations in the study design and method and inconsistency; 5 = down-grading for limitations in study design and method and inaccuracy; 6 = down-grading for limitations in study design and method, inconsistency and inaccuracy. **f** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.

From evidence to recommendation

- When formulating the recommendation (direction and strength) for exercise therapy for indication 2, the guideline panel additionally considered the following. See also the assessment form from evidence to recommendation for exercise therapy for indication 2 in the appendix to this Note.
- The desired effects (improvement in quality of life and degree of physical activity) of exercise therapy are present, while the undesirable effects (increased pain, disease activity and/or radiological damage) were in favour of the exercise therapy. Based on this, the guideline panel estimated that the desired effects outweigh the undesirable effects.
- How much patients value exercise therapy will likely differ from patient to patient. The guideline panel estimates that most patients will have a positive view of exercise therapy due to its favourable effects and because patients can easily incorporate exercise therapy into their daily lives.
- The costs of exercise therapy for the patient depend on the reimbursement by the health insurance company and the current government regulations regarding medical expenses (see Rijksoverheid.nl) but in general remain limited because the physical therapist only gives supervision for a short time. There are few to no costs associated with exercise therapy for the physical therapist, based on the assumption that the required exercise equipment is already present.
- From the social perspective and without taking into account long-term preventive health effects, a sustained exercise programme lasting two years appears to yield insufficient improvement in health valuation to justify the additional costs (ICER € 6,7000 per QALY)20, with the quality of evidence being given a score of 11 on a scale of 19 (with 19 being the highest quality of evidence) according to the CHEC list for economic evaluations. However, according to this guideline a treatment duration of three to six months is used for indication 2, and the cost-effectiveness of this is as yet unknown.
- The guideline panel deems that implementing the intervention in daily practice is acceptable and feasible because the intervention is viewed as the most indicated treatment option and no specific resources are required.

Sources

1. Baillet A, Payraud E, Niderprim VA, Nissen MJ, Allenet B, François P, et al. A dynamic exercise programme to improve patients' disability in rheumatoid arthritis: a prospective randomized controlled trial. Rheumatology (Oxford). 2009 Apr;48(4):410-5.
2. Baslund B, Lyngberg K, Andersen V, Halkjaer Kristensen J, Hansen M, Klokker M, et al. Effect of 8 wk of bicycle training on the immune system of patients with rheumatoid arthritis. J Appl Physiol. 1993;75:1691-5.
3. Bearne LM, Scott DL, Hurley MV. Exercise can reverse quadriceps sensorimotor dysfunction that is associated with rheumatoid arthritis without exacerbating disease activity. Rheumatology (Oxford). 2002 Feb;41(2):157-66.
4. Bilberg A, Ahlmén M, Mannerkorpi K. Moderately intensive exercise in a temperate pool for patients with rheumatoid arthritis: a randomized controlled study. Rheumatology (Oxford). 2005 Apr;44(4):502-8.
5. Breedland I, van Scheppingen C, Leijsma M, Verheij-Jansen NP, van Weert E. Effects of a group-based exercise and educational program on physical performance and disease self-management in rheumatoid arthritis: a randomized controlled study. Phys Ther. 2011 Jun;91(6):879-93.
6. Da Silva KN, Teixeira LE, Imoto AM, Atallah AN, Peccin MS, Trevisani VF. Effectiveness of sensorimotor training in patients with rheumatoid arthritis: a randomized controlled trial. Rheumatol Int. 2013 Sep;33(9):2269-75.
7. de Jong Z, Munneke M, Zwinderman AH, Kroon HM, Jansen A, Ronday KH, et al. Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. Arthritis Rheum. 2003;48(9):2415-24.
8. Flint-Wagner HG, Lisse J, Lohman TG, Going SB, Guido T, Cussler E, Gates D, Yocum DE. Assessment of a sixteen-week training program on strength, pain, and function in rheumatoid arthritis patients. J Clin Rheumatol. 2009 Jun;15(4):165-71.

9. Häkkinen A, Häkkinen K, Hannonen P. Effects of strength training on neuromuscular function and disease activity in patients with recent-onset inflammatory arthritis. Scand J Rheumatol. 1994;23(5):237-42.
10. Hansen TM, Hansen G, Langgaard AM, Rasmussen JO. Longterm physical training in rheumatoid arthritis. A randomized trial with different training programs and blinded observers. Scand J Rheumatol. 1993;22(3):107-12.
11. Harkcom TM, Lampman RM, Banwell BF, Castor CW. Therapeutic value of graded aerobic exercise training in rheumatoid arthritis. Arthr Rheum. 1985;28(1):32-9.
12. Lemmey AB, Marcora SM, Chester K, Wilson S, Casanova F, Maddison PJ. Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial. Arthritis Rheum. 2009 Dec 15;61(12):1726-34.
13. Lyngberg KK, Harreby M, Bentzen H, Frost B. Elderly rheumatoid arthritis on steroid treatment tolerate physical training without an increase in disease activity. Arch Phys Med Rehab. 1994;75:1189-95.
14. McMeeken J, Stillman B, Story I, Kent P, Smith J. The effects of knee extensor and flexor muscle training on the timed-up-and-go test in individuals with rheumatoid arthritis. Physiother Res Int. 1999;4(1):55-67.
15. Minor MA, Hewett JE, Webel RR, Anderson SK, Kay DR. Efficacy of physical conditioning exercise in patients with rheumatoid arthritis and osteoarthritis. Arthritis Rheum. 1989;32(11):1396-405.
16. Sanford-Smith S, Mackay-Lyons M, Nunes-Clement S. Therapeutic benefit of aquaerobics for individuals with rheumatoid arthritis. Physiotherapy Canada 1998;Winter:40–6.
17. Siqueira US, Orsini Valente LG, de Mello MT, Szejnfeld VL, Pinheiro MM. Effectiveness of aquatic exercises in women with rheumatoid arthritis: a randomized, controlled, 16-week intervention – the HydRA Trial. Am J Phys Med Rehabil. 2017 Mar;96(3):167-75.
18. Strasser B, Leeb G, Strehblow C, Schobersberger W, Haber P, Cauza E. The effects of strength and endurance training in patients with rheumatoid arthritis. Clin Rheumatol. 2011 May;30(5):623-32.
19. van den Ende CHM, Hazes JMW, Le Cessie S, Mulder WJ, Belfor DG, Breedveld FC, et al. Comparison of high and low intensity training in well controlled rheumatoid arthritis. Results of a randomized clinical trial. Ann Rheum Dis. 1996;55(11):798-805.
20. van den Hout WB, de Jong Z, Munneke M, Hazes JM, Breedveld FC, Vliet Vlieland TP. Cost-utility and cost-effectiveness analyses of a long-term, high-intensity exercise program compared with conventional physical therapy in patients with rheumatoid arthritis. Arthritis Rheum. 2005 Feb 15;53(1):39-47.

Note 13. Exercise therapy for indication 3

Clinical question

Is exercise therapy recommended for patients with indication 3?

Complete clinical question according to PICO

To answer this clinical question, a joint PICO clinical question was formulated for indication 1, 2 and 3 (see Note 10).

Search strategy

A joint search was conducted for indication 1, 2 and 3 (see Note 10).

Literature found

No studies were found for indication 3.

Description of studies

Not applicable: no studies were found where the effectiveness of exercise therapy was evaluated in patients with a complex need for assistance.

Effectiveness and quality of evidence

Not applicable.

From evidence to recommendation

When formulating the direction and strength of the recommendation for exercise therapy for indication 3, the guideline panel considered the following. See also the assessment form from evidence to recommendation for exercise therapy for indication 3 in the appendix to this Note.

- Although no estimated effects of exercise therapy for indication 3 are available, the guideline panel assumes that the desired effects (improvement of the quality of life, degree of physical activity and/or fatigue) of exercise therapy are likely and outweigh the undesirable effects (increased pain, disease activity and/or radiological damage).
- How much patients value exercise therapy will likely differ from patient to patient. The guideline panel estimates that the majority of patients will have a positive view of exercise therapy because there are few alternatives and because patients can easily incorporate exercise therapy into their daily lives.
- The costs of exercise therapy for the patient depend on the current government regulations regarding medical expenses (see Rijksoverheid.nl). There are few to no costs associated with exercise therapy for the physical therapist, based on the assumption that the required exercise equipment is already present.
- The guideline panel deems that implementing this intervention in daily practice is acceptable and feasible, because the intervention is viewed as the most indicated treatment option and no specific resources are required.

Sources

Not applicable.

Note 14. Frequency, intensity, type and duration of the exercise therapy and red and yellow flags

Clinical question

Which frequency, intensity, type and duration of the exercise therapy interventions are recommended for patients with RA?

Complete clinical question according to PICO

Which frequency, intensity, type and duration of the exercise therapy interventions (I) are recommended, compared to exercise therapy interventions with a different frequency, intensity, type and duration (C) for patients with RA (P) to improve their quality of life, physical functioning, pain, fatigue, aerobic capacity, muscle strength, range of motion, disease activity, radiological damage and work productivity (O)?

Search strategy

On March 3, 2017, the KNGF conducted a search on a summary of the literature (i.e. systematic review) and randomised controlled studies on exercise therapy in patients with RA. Details of this search operation are described in table 14.1. The search terms (general for all FITT principles) are included in the attachment to this Note.

Table 14.1. Selection criteria for systematic review for FITT principles.

Type of study	RCTs
Type of patient	adults diagnosed with rheumatoid arthritis based on the ARA or ACR/EULAR classification criteria
Type of intervention	any form of exercise therapy
Type of comparison	any form of exercise therapy where there is a difference in duration, frequency, intensity, build-up, type of exercises or form
Type of outcome	crucial outcome measures: quality of life, physical functioning, pain*, fatigue important outcome measures: aerobic capacity, muscle strength, range of motion, disease activity*, radiological damage*, work productivity
Type of timeline	immediately after the intervention

** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.*

Literature found

The literature search yielded 1837 references. Twelve randomised controlled studies met the inclusion criteria for answering the clinical question regarding the FITT principles.1–12 The results of the reviews of the frequency, intensity, type and duration of the exercise therapy can be found in Note 15, 16, 17 and 18, respectively. General recommendations for exercise therapy are also described in Note 19.

Sources

1. Bostrom C, Harms-Ringdahl K, Karreskog H, Nordemar R. Effects of static and dynamic shoulder rotator exercises in women with rheumatoid arthritis: a randomised comparison of impairment, disability, handicap, and health. Scand J Rheumatol. 1998;27(4):281-90.
2. Ekdahl C, Andersson SI, Moritz U, Svensson B. Dynamic versus static training in patients with rheumatoid arthritis. Scand J Rheumatol. 1990;19(1):17-26.
3. van den Ende CHM, Hazes JMW, le Cessie S, Mulder WJ, Belfor DG, Breedveld FC, Dijkmans BA. Comparison of high and low intensity training in well controlled rheumatoid arthritis. Results of a randomized clinical trial. Ann Rheum Dis. 1996;55(11):798-805.
4. van den Ende CHM, Breedveld FC, le Cessie S, Dijkmans BAC, de Mug AW, Hazes JMW. Effect of intensive exercise on patients with active rheumatoid arthritis: a randomised clinical trial. Ann Rheum Dis. 2000;59:615-21.
5. Harkcom TM, Lampman RM, Banwell BF, Castor CW. Therapeutic value of graded aerobic exercise training in rheumatoid arthritis. Arthr Rheum. 1985;28(1):32-9.
6. Minor MA, Hewett JE, Webel RR, Anderson SK, Kay DR. Efficacy of physical conditioning exercise in patients with rheumatoid arthritis and osteoarthritis. Arthritis Rheum. 1989;32(11):1396-405.
7. Dogu B, Sirzai H, Yilmaz F, Polat B, Kuran B. Effects of isotonic and isometric hand exercises on pain, hand functions, dexterity and quality of life in women with rheumatoid arthritis. Rheumatol Int. 2013;33(10):2625-30,
8. Cima SR, Barone A, Porto JM, de Abreu DC. Strengthening exercises to improve hand strength and functionality in rheumatoid arthritis with hand deformities: a randomized, controlled trial. Rheumatol Int. 2013;33(3):725-32.
9. Lamb SE, Williamson EM, Heine PJ, Adams J, Dosanjh S, Dritsaki M, et al. Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet. 2015;385(9966):421-9.
10. O'Brien AV, Jones P, Mullis R, Mulherin D, Dziedzic K. Conservative hand therapy treatments in rheumatoid arthritis-a randomized controlled trial. Rheumatology (Oxford). 2006;45(5):577-83.
11. Minor MA, Hewett JE, Webel RR, Anderson SK, Kay DR. Efficacy of physical conditioning exercise in patients with rheumatoid arthritis and osteoarthritis. Arthritis and Rheumatism 1989;32(11):1396-405.
12. Siqueira US, Orsini Valente LG, de Mello MT, Szejnfeld VL, Pinheiro MM. Effectiveness of aquatic exercises in women with rheumatoid arthritis: a randomized, controlled, 16-week intervention-the HydRA Trial. Am J Phys Med Rehabil. 2017 Mar;96(3):167-175.

Note 15. Frequency

Clinical question

Which frequency of exercise therapy is recommended for patients with RA?

Complete clinical question according to PICO

To answer this clinical question, a joint PICO clinical question was formulated for the frequency, intensity, type and duration of the exercise therapy (see Note 14).

Search strategy

A joint search on the frequency, intensity, type and duration of the exercise therapy was carried out (see Note 14).

Literature found

No randomised controlled studies were found in which a comparison was done in the frequency of exercise therapy (see Note 14). To be able to formulate a recommendation nevertheless about the frequency, a subgroup analysis was conducted with the studies included for the clinical question about exercise therapy in order to determine which frequency yields the optimal result.

Description of studies
Of the 19 included studies on the effectiveness of exercise therapy, ten studies had a frequency of twice per week [3-7, 10, 12-14, 18], seven studies had a frequency of three times per week [8,9.11,15-17,19] and two studies had a frequency of four to five times per week.[1,2] The characteristics of the studies are described in Note 10.

Effectiveness and quality of evidence
The assessment of the study design and execution per study is included in the appendix to this Note.

Below follows a description of the effectiveness of exercise therapy in relation to its frequency and the quality of evidence for each outcome measure. See also the GRADE profiles of exercise therapy in various frequencies in table 15.1, 15.2 and 15.3.

Desired effects

Crucial outcome measures

a) 'Quality of life' outcome measure:
   - There is a large effect (SMD = 0.77; 95%-CI = -0.08-1.62) of exercise therapy with a frequency of twice per week (2 studies) on the quality of life for patients with RA compared to the control group. The effect of exercise therapy with a frequency of three times per week (0 studies) and of four to five times per week (1 study; SMD is unavailable) is unknown.
   - The quality of evidence for the 'quality of life' outcome measure with a frequency of twice per week was lowered by two levels to 'low quality of evidence', given the limitations, contradictory results (inconsistency) and small number of patients (inaccuracy). The quality of evidence for the 'quality of life' outcome measure with a frequency of four to five times per week was lowered by two levels to 'low quality of evidence', given the limitations, contradictory results (inconsistency) and small number of patients (inaccuracy).

b) 'Physical functioning' outcome measure:
   - There is a large effect (SMD = 0.50; 95%-CI = 0.19-0.82) of exercise therapy with a frequency of twice per week (8 studies) on physical functioning of patients with RA compared to the control group. The effect of exercise therapy with a frequency of three times per week (7 studies) is slight (SMD = 0.28; 95%-BI = -0.01-0.57) and the effect of exercise therapy with a frequency of four to five times per week (1 study) is unknown (SMD is unavailable).
   - The quality of evidence for the 'physical functioning' outcome measure with a frequency of twice per week was lowered by one level to 'acceptable quality of evidence', given the contradictory results (inconsistency). The quality of evidence for the 'physical functioning' outcome measure with a frequency of three times per week was lowered by two levels to 'low quality of evidence', given the limitations of the study design and execution and the small number of patients (inaccuracy).

c) 'Fatigue' outcome measure:
   - The effect of exercise therapy with a frequency of twice per week, three times per week or four to five times per week on fatigue is unknown, as is the quality of evidence (0 studies).

d) 'Pain' outcome measure:
   - There is a moderate effect (SMD = 0.42; 95%-CI = 0.40-1.24) of exercise therapy with a frequency of twice per week (2 studies) on pain in patients with RA compared to the control group. The effect of exercise therapy with a frequency of three times per week (1 study; SMD is unavailable) and of four to five times per week (0 studies) on pain is unknown.
   - The quality of evidence for the 'pain' outcome measure with a frequency of twice per week was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and the small number of patients (inaccuracy). The quality of evidence for the 'pain' outcome measure with a frequency of three times per week was lowered by two levels to 'very low quality of evidence', given the limitations of the study design and execution, contradictory results (inconsistency) and small number of patients (inaccuracy).

Important outcome measures

a) 'Aerobic capacity' outcome measure:
   - There is a moderate effect (SMD = 0.44; 95%-CI = 0.25-0.64) of exercise therapy with a frequency of twice per week (5 studies) on aerobic capacity in patients with RA compared to the control group. The effect of exercise therapy with a frequency of three times per week (4 studies) is large (SMD = 0.59; 95%-BI = -0.25-0.92), and the effect of exercise therapy with a frequency of four to five times per week (2 studies) is also large (SMD = 0.61; 95%- BI = 0.08-1.14).
   - The quality of evidence for the 'aerobic capacity' outcome measure with a frequency of twice per week is high (and was not lowered). The quality of evidence for the 'aerobic capacity' outcome measure with a frequency of three times per week was lowered by two levels to 'low quality of evidence', given the limitations of the study design and method and the small number of patients (inaccuracy). The quality of evidence for the 'aerobic capacity' outcome measure with a frequency of four to five times per week was lowered by one level to 'acceptable quality of evidence', given the small number of patients (inaccuracy).

b) 'Muscle strength' outcome measure:
   - There is a large effect (SMD = 0.72; 95%-CI = 0.20-1.23) of exercise therapy with a frequency of twice per week (9 studies) on the muscle strength of patients with RA compared to the control group. The effect of exercise therapy with a frequency of three times per week (2 studies) is also large (SMD = 0.53; 95%-BI = -0.02-1.07). The effect of exercise therapy with a frequency of four to five times per week on muscle strength is unknown (0 studies).
   - The quality of evidence for the 'muscle strength' outcome measure with a frequency of twice per week was lowered by two levels to 'low quality of evidence', given the limitations in study design and method and inconsistency. The quality of evidence for the 'muscle strength' outcome measure with a frequency of three times per week was lowered to 'low quality of evidence', given the limitations of the study design and method and the small number of patients (inaccuracy).

c) 'Range of motion' outcome measure:
   - The effect of exercise therapy with a frequency of twice per week (1 study) on the range of motion in patients with RA is unknown (SMD is unavailable). The effect of exercise therapy with a frequency of three times per week (1 study) on the range of motion in patients with RA is also unknown (SMD is unavailable). The effect of exercise therapy with a frequency of four to five times per week is unknown (0 studies).
   - The quality of evidence for the 'range of motion' outcome measure with a frequency of twice per week was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and the small number of patients (inaccuracy). The quality of evidence for the 'range of motion' outcome measure with a frequency of three times per week was also lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and the small number of patients (inaccuracy).

d) 'Work productivity' outcome measure:
   - The effectiveness and quality of evidence could not be determined (0 studies).

Undesirable effects

a) 'Disease activity' outcome measure:
   - There is a moderate effect (SMD = 0.33; 95%-CI = -0.28-0.95) of exercise therapy with a frequency of twice per week (4 studies) on disease activity in patients with RA compared to the control group. The effect of exercise therapy with a frequency of three times per week (3 studies) is slight (SMD = 0.04; 95%-BI = -0.70-0.79) and the effect of exercise therapy with a frequency of four to five times per week (2 studies) is also slight (SMD = 0.06; 95%-BI = -1.64-1.77).
   - The quality of evidence for the 'disease activity' outcome measure with a frequency of twice per week was lowered by one level to 'acceptable quality of evidence' given the inconsistency. The quality of evidence for the 'disease activity' outcome measure with a frequency of three times per week was lowered by three levels to 'very low quality of evidence', given the limitations of the study design and method, contradictory results (inconsistency) and small number of patients (inaccuracy). The quality of evidence for the 'disease activity' outcome measure with a frequency of four to five times per week was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and the small number of patients (inaccuracy).

b) 'Radiological damage' outcome measure:
- There is a slight effect (SMD = -0.09; 95%-CI = 0.14-0.31) of exercise therapy with a frequency of twice per week (2 studies) on radiological damage in patients with RA compared to the control group. The effect of exercise therapy with a frequency of three or a frequency of four to five times per week is unknown (0 studies).
- The quality of evidence for the 'radiological damage' outcome measure with a frequency of twice per week was lowered by one level to 'acceptable quality of evidence', given the small number of patients (inaccuracy).

Table 15.1 GRADE profile of exercise therapy with a frequency of twice per week.

	Number of studies	GRADE+					Number of patients		Estimated effect	Quality of evidence
		Limitations in study design and execution[a]	Inconsistency[b]	Indirectness	Inaccuracy[c]	Other	Exercise therapy	Control	Standardized mean difference (95%-CI)[d]	very low / low / acceptable / high[e]
Desired effects	**Crucial outcome measures**									
	Quality of life									
	n = 2	moderate	yes, I^2 = 81%	no	yes, *n* = 145	no	71	74	0,77 (-0,08 to 1,62)	low (3)
	Physical functioning									
	n = 8	moderate	yes, I^2 = 60%	no	no, *n* = 450	no	223	227	0,50 (0,19 to 0,82)	moderate (1)
	Fatigue									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Pain									
	n = 2	moderate	yes, I^2 = 88%	no	yes, *n* = 195	no	98	95	0,42 (-0,40 to 1,24)	low (3)
	Important outcome measures									
	Aerobic capacity									
	n = 5	moderate	no, I^2 = 0%	no	no, *n* = 423	no	207	215	0,44 (0,25 to 0,64)	high
	Muscle strength									
	n = 9	high	yes, I^2 = 86%	no	no, *n* = 611	no	296	315	0,72 (0,20 to 1,23)	low (4)
	Range of motion									
	n = 1	moderate	no	no	yes, *n* = 43	no	20	23	no significant effect	low (3)
	Work productivity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Undesirable effects[f]	**Disease activity**									
	n = 4	moderate	yes, I^2 = 83%	no	no, *n* = 422	no	206	216	0,33 (-0,28 to 0,95)	moderate (1)
	Radiological damage									
	n = 2	moderate	no, I^2 = 0%	no	yes, *n* = 305	no	147	158	-0,09 (-0,14 to 0,31)	moderate (2)

n/a: not applicable. **a** Limitations in study design and execution were low in the case of random assignment + allocation concealed + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading took place with a high score. **b** Down-grading took place with I2 > 40%. **c** Down-grading took place in the event of a dichotomous outcome measure with n < 300 and in the case of a continuous outcome measure with *n* < 400. **d** A positive standardised mean difference (SMD) reflects a benefit for the intervention group compared to the control group. If one study measured the respective outcome measure, the results from this study are described. An SMD of < 0.3 is considered as a slight effect of the intervention; 0.3-0.5 as a moderate effect and > 0.5 as a large effect. **e** 1 = down-grading for inconsistency; 2 = down-grading for inaccuracy; 3 = down-grading for inconsistency and inaccuracy; 4 = down-grading for limitations in the study design and method and inconsistency; 5 = down-grading for limitations in study design and method and inaccuracy; 6 = down-grading for limitations in study design and method, inconsistency and inaccuracy. **f** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.

Table 15.2. GRADE profile of exercise therapy with a frequency of three times per week.

	Number of studies	GRADE+					Number of patients		Estimated effect	Quality of evidence
		Limitations in study design and execution[a]	Inconsistency[b]	Indirectness	Inaccuracy[c]	Other	Exercise therapy	Control	Standardized mean difference (95%-CI)[d]	very low / low / acceptable / high[e]
Desired effects	**Crucial outcome measures**									
	Quality of life									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Physical functioning									
	n = 7	high	no, I^2 = 27%	no	yes, *n* = 176	no	148	128	0,28 (-0,01 to 0,57)	low (5)
	Fatigue									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Pain									
	n = 1	high	no	no	yes, *n* = 24	no	16	8	no significant effect	very low (6)
	Important outcome measures									
	Aerobic capacity									
	n = 4	high	no, I^2 = 0%	no	yes, *n* = 148	no	78	68	0,59 (0,25 to 0,92)	low (5)
	Muscle strength									
	n = 2	high	no, I^2 = 18%	no	yes, *n* = 74	no	41	33	0,53 (-0,02 to 1,07)	low (5)
	Range of motion									
	n = 1	moderate	no	no	yes, *n* = 50	no	25	25	A significant effect was found in the benefit of exercise therapy	low (3)
	Work productivity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Undesirable effects[f]	**Disease activity**									
	n = 3	high	yes, I^2 = 54%	no	yes, *n* = 80	no	40	40	0,04 (-0,70 to 0,79)	very low (6)
	Radiological damage									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

n/a: not applicable. **a** Limitations in study design and execution were low in the case of random assignment + allocation concealed + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading took place with a high score. **b** Down-grading took place with I2 > 40%. **c** Down-grading took place in the event of a dichotomous outcome measure with n < 300 and in the case of a continuous outcome measure with *n* < 400. **d** A positive standardised mean difference (SMD) reflects a benefit for the intervention group compared to the control group. If one study measured the respective outcome measure, the results from this study are described. An SMD of < 0.3 is considered as a slight effect of the intervention; 0.3-0.5 as a moderate effect and > 0.5 as a large effect. **e** 1 = down-grading for inconsistency; 2 = down-grading for inaccuracy; 3 = down-grading for inconsistency and inaccuracy; 4 = down-grading for limitations in the study design and method and inconsistency; 5 = down-grading for limitations in study design and method and inaccuracy; 6 = down-grading for limitations in study design and method, inconsistency and inaccuracy. **f** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.

Table 15.3. The effect of exercise therapy with a frequency of four to five times per week.

	Number of studies	GRADE+					Number of patients		Estimated effect	Quality of evidence
		Limitations in study design and execution[a]	Inconsistency[b]	Indirectness	Inaccuracy[c]	Other	Exercise therapy	Control	Standardized mean difference (95%-CI)[d]	very low / low / acceptable / high[e]
Desired effects	**Crucial outcome measures**									
	Quality of life									
	n = 1	low	Unclear	no	yes, *n* = 48	no	25	23	no significant effect	low (3)
	Physical functioning									
	n = 1	low	Unclear	no	yes, *n* = 48	no	25	23	no significant difference	low (3)
	Fatigue									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Pain									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Important outcome measures									
	Aerobic capacity									
	n = 2	moderate	no, I^2 = 0%	no	yes, *n* = 58	no	29	29	0,61 (0,08 to 1,14)	acceptable (2)
	Muscle strength									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Range of motion									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Work productivity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Undesirable effects[f]	**Disease activity**									
	n = 2	moderate	yes, I^2 = 81%	no	yes, *n* = 58	no	29	29	0,06 (-1,64 to 1,77)	low (3)
	Radiological damage									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

n/a: not applicable. **a** Limitations in study design and execution were low in the case of random assignment + allocation concealed + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading took place with a high score. **b** Down-grading took place with I2 > 40%. **c** Down-grading took place in the event of a dichotomous outcome measure with n < 300 and in the case of a continuous outcome measure with *n* < 400. **d** A positive standardised mean difference (SMD) reflects a benefit for the intervention group compared to the control group. If one study measured the respective outcome measure, the results from this study are described. An SMD of < 0.3 is considered as a slight effect of the intervention; 0.3-0.5 as a moderate effect and > 0.5 as a large effect. **e** 1 = down-grading for inconsistency; 2 = down-grading for inaccuracy; 3 = down-grading for inconsistency and inaccuracy; 4 = down-grading for limitations in the study design and method and inconsistency; 5 = down-grading for limitations in study design and method and inaccuracy; 6 = down-grading for limitations in study design and method, inconsistency and inaccuracy. **f** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.

From evidence to recommendation

When formulating the direction and strength of the recommendation for exercise therapy for indication 1, the guideline panel considered the following.

Based on the magnitude of the estimated effects and the quality of evidence, the guideline panel believes that a frequency of twice per week of supervised exercise therapy is preferable (for indication 2), supplemented by exercises performed independently. Here it must be noted that the supervision during the treatment period must be reduced in consultation with the patient, with the emphasis shifting to independent exercising and physical activity. Based on the ACSM guidelines [20], it should be added that muscle strength or functional exercises and/or activities are recommended to be done daily but at least two days per week and aerobic exercises and/or activities preferably daily but at least five days per week for at least 30 minutes per time, also in order to comply with the 'Dutch physical activity guidelines' [21].

- How much patients value a certain frequency and which frequency they prefer will likely differ from patient to patient. The guideline panel estimates that the majority of patients will have a positive view of exercise therapy with a frequency of twice per week.
- The potential costs for the patient are more favourable with a frequency of twice per week supervised exercise therapy than at higher frequencies (3-5 times per week).
- The guideline panel deems implementing exercise therapy with a frequency of twice per week in daily practice to be acceptable and feasible, because this frequency is viewed as the most indicated treatment frequency.

Sources

1. Baillet A, Payraud E, Niderprim VA, Nissen MJ, Allenet B, François P, et al. A dynamic exercise programme to improve patients' disability in rheumatoid arthritis: a prospective randomized controlled trial. Rheumatology (Oxford). 2009 Apr;48(4):410-5.
2. Baslund B, Lyngberg K, Andersen V, Halkjaer Kristensen J, Hansen M, Klokker M, et al. Effect of 8 wk of bicycle training on the immune system of patients with rheumatoid arthritis. J Appl Physiol. 1993;75:1691-5.
3. Bearne LM, Scott DL, Hurley MV. Exercise can reverse quadriceps sensorimotor dysfunction that is associated with rheumatoid arthritis without exacerbating disease activity. Rheumatology (Oxford). 2002 Feb;41(2):157-66.
4. Bilberg A, Ahlmén M, Mannerkorpi K. Moderately intensive exercise in a temperate pool for patients with rheumatoid arthritis: a randomized controlled study. Rheumatology (Oxford). 2005 Apr;44(4):502-8.
5. Breedland I, van Scheppingen C, Leijsma M, Verheij-Jansen NP, van Weert E. Effects of a group-based exercise and educational program on physical performance and disease self-management in rheumatoid arthritis: a randomized controlled study. Phys Ther. 2011 Jun;91(6):879-93.
6. Da Silva KN, Teixeira LE, Imoto AM, Atallah AN, Peccin MS, Trevisani VF. Effectiveness of sensorimotor training in patients with rheumatoid arthritis: a randomized controlled trial. Rheumatol Int. 2013 Sep;33(9):2269-75.
7. de Jong Z, Munneke M, Zwinderman AH, Kroon HM, Jansen A, Ronday KH, et al. Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. Arthritis Rheum. 2003;48(9):2415-24.
8. Flint-Wagner HG, Lisse J, Lohman TG, Going SB, Guido T, Cussler E, Gates D, Yocum DE. Assessment of a sixteen-week training program on strength, pain, and function in rheumatoid arthritis patients. J Clin Rheumatol. 2009 Jun;15(4):165-71,
9. Häkkinen A, Häkkinen K, Hannonen P. Effects of strength training on neuromuscular function and disease activity in patients with recent-onset inflammatory arthritis. Scand J Rheumatol. 1994;23(5):237-42.
10. Hansen TM, Hansen G, Langgaard AM, Rasmussen JO. Longterm physical training in rheumatoid arthritis. A randomized trial with different training programs and blinded observers. Scand J Rheumatol. 1993;22(3):107-12.
11. Harkcom TM, Lampman RM, Banwell BF, Castor CW. Therapeutic value of graded aerobic exercise training in rheumatoid arthritis. Arthr Rheum. 1985;28(1):32-9.
12. Lemmey AB, Marcora SM, Chester K, Wilson S, Casanova F, Maddison PJ. Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial. Arthritis Rheum. 2009 Dec 15;61(12):1726-34.
13. Lyngberg KK, Harreby M, Bentzen H, Frost B. Elderly rheumatoid arthritis on steroid treatment tolerate physical training without an increase in disease activity. Arch Phys Med Rehab. 1994;75:1189-95.
14. McMeeken J, Stillman B, Story I, Kent P, Smith J. The effects of knee extensor and flexor muscle training on the timed-up-and-go test in individuals with rheumatoid arthritis. Physiother Res Int. 1999;4(1):55-67.
15. Minor MA, Hewett JE, Webel RR, Anderson SK, Kay DR. Efficacy of physical conditioning exercise in patients with rheumatoid arthritis and osteoarthritis. Arthritis Rheum. 1989;32(11):1396-405.
16. Sanford-Smith S, Mackay-Lyons M, Nunes-Clement S. Therapeutic benefit of aquaerobics for individuals with rheumatoid arthritis. Physiotherapy Canada 1998;Winter:40–6.
17. Siqueira US, Orsini Valente LG, de Mello MT, Szejnfeld VL, Pinheiro MM. Effectiveness of aquatic exercises in women with rheumatoid arthritis: a randomized, controlled, 16-week intervention – the HydRA Trial. Am J Phys Med Rehabil. 2017 Mar;96(3):167-75.
18. Strasser B, Leeb G, Strehblow C, Schobersberger W, Haber P, Cauza E. The effects of strength and endurance training in patients with rheumatoid arthritis. Clin Rheumatol. 2011 May;30(5):623-32.
19. van den Ende CHM, Hazes JMW, Le Cessie S, Mulder WJ, Belfor DG, Breedveld FC, et al. Comparison of high and low intensity training in well controlled rheumatoid arthritis. Results of a randomized clinical trial. Ann Rheum Dis. 1996;55(11):798-805.

20. American College of Sports Medicine. Guidelines for Exercise Testing and Prescription. 10th Edition. Lippincott William and Wilkins; 2017.
21. Exercise guidelines 2017. Summary. The Hague: Gezondheidsraad [Dutch Health Council]; 2017. Available at https://www.gezondheidsraad.nl/sites/default/files/grpublication/samenvatting_beweegrichtlijnen_2017_1.pdf

Note 16. Intensity

Clinical question

Which intensity of exercise therapy is recommended for patients with RA?

Complete clinical question according to PICO

To answer this clinical question, a joint PICO clinical question was formulated for the frequency, intensity, type and duration of exercise therapy (see Note 14).

Search strategy

A joint search on the frequency, intensity, type and duration of exercise therapy was carried out (see Note 14).

Literature found

The literature search yielded 1837 references. Four randomised controlled studies met the inclusion criteria for answering the clinical question regarding the intensity of the exercise therapy.[1-4] The information from these studies was supplemented with information from the ACSM guideline.[5]

Description of studies

In four studies a high-intensity (dynamic) exercise programme was compared with an exercise programme with a lower intensity.[1-4] Note 14 contains an explanation of how these studies were included.

Effectiveness and quality of evidence

The assessment of the study design and execution of the selected articles is included in the appendix to this Note.

Below follows a description of the effectiveness of exercise therapy in relation to its intensity and the quality of evidence for each outcome measure. See also the GRADE profile of the intensity of exercise therapy in table 16.1.

Desired effects

Crucial outcome measures

a) 'Quality of life' outcome measure (0 studies):
   - The effect and the quality of evidence of high-intensity exercise therapy compared to lower-intensity exercise therapy on quality of life is unknown.

b) 'Physical functioning' outcome measure (3 studies):
   - The effect of high-intensity exercise therapy compared to lower-intensity exercise therapy on physical functioning is unknown (SMD unavailable).
   - The quality of evidence for the 'physical functioning' outcome measure was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and the small number of patients (inaccuracy).

c) 'Fatigue' outcome measure (0 studies):
   - The effect of high-intensity exercise therapy compared to lower-intensity exercise therapy on fatigue is unknown.

d) 'Pain' outcome measure (4 studies):
   - The effect of high-intensity exercise therapy compared to lower-intensity exercise therapy on pain is unknown (SMD unavailable).
   - The quality of evidence for the 'pain' outcome measure was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and small number of patients (inaccuracy).

Important outcome measures

a) 'Aerobic capacity' outcome measure (2 studies):
   - The effect and the quality of evidence of high-intensity exercise therapy compared to lower-intensity exercise therapy on the aerobic capacity is unknown (SMD unavailable).
   - The quality of evidence for the 'aerobic capacity' outcome measure was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and small number of patients (inaccuracy).

b) 'Muscle strength' outcome measure (4 studies):
   - The effect of high-intensity exercise therapy compared to lower-intensity exercise therapy on muscle strength is unknown (SMD unavailable).
   - The quality of evidence for the 'muscle strength' outcome measure was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and small number of patients (inaccuracy).

c) 'Range of motion' outcome measure (3 studies):
   - The effect of high-intensity exercise therapy compared to lower-intensity exercise therapy on range of motion is unknown (SMD unavailable).
   - The quality of evidence for the 'range of motion' outcome measure was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and small number of patients (inaccuracy).

d) 'Work productivity' outcome measure (0 studies):
   - The effect of high-intensity exercise therapy compared to lower-intensity exercise therapy on pain is unknown (SMD unavailable).
   - The quality of evidence for the 'pain' outcome measure was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and small number of patients (inaccuracy).

Undesirable effects

a) 'Disease activity' outcome measure (4 studies):
   - The effect of high-intensity exercise therapy compared to lower-intensity exercise therapy on disease activity is unknown (SMD unavailable).
   - The quality of evidence for the 'disease activity' outcome measure was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and small number of patients (inaccuracy).

b) 'Radiological damage' outcome measure (1 study):
   - The effect of high-intensity exercise therapy compared to lower-intensity exercise therapy on radiological damage is unknown (SMD unavailable).
   - The quality of evidence for the 'radiological damage' outcome measure was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and the small number of patients (inaccuracy).

Table 16.1 GRADE profile of the intensity of exercise therapy.

	Number of studies	GRADE+					Number of patients		Estimated effect	Quality of evidence
		Limitations in study design and execution[a]	Inconsistency[b]	Indirectness	Inaccuracy[c]	Other	Exercise therapy	Control	Standardized mean difference (95%-CI)[d]	very low / low / acceptable / high[e]
Desired effects	**Crucial outcome measures**									
	Quality of life									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Physical functioning									
	n = 3	low	unknown	no	yes, *n* = 129	no	70	59	A significant difference was found in one study. No difference was found in two studies.	low (3)
	Fatigue									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Pain									
	n = 4	low	unknown	no	yes, *n* = 195	no	unknown	unknown	A significant difference was not found in any of the studies.	low (3)
	Important outcome measures									
	Aerobic capacity									
	n = 2	low	unknown	no	yes, *n* = 117	no	unknown	unknown	A significant difference was found in both studies.	low (3)
	Muscle strength									
	n = 4	low	unknown	no	yes, *n* = 195	no	unknown	unknown	A significant difference was found in three studies. No difference was found in one study.	low (3)
	Range of motion									
	n = 3	low	unknown	no	yes, *n* = 181	no	unknown	unknown	A significant difference was found in two studies. No difference was found in one study.	low (3)
	Work productivity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Undesirable effects[f]	**Disease activity**									
	n = 4	low	unknown	no	yes, *n* = 195	no	unknown	unknown	No difference was found in any of the four studies.	low (3)
	Radiological damage									
	n = 1	low	unknown	no	yes, *n* = 50	no	25	25	Study shows no difference.	low (3)

n/a: not applicable. **a** Limitations in study design and execution were low in the case of random assignment + allocation concealed + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading took place with a high score. **b** Down-grading took place with I2 > 40%. **c** Down-grading took place in the event of a dichotomous outcome measure with n < 300 and in the case of a continuous outcome measure with *n* < 400. **d** A positive standardised mean difference (SMD) reflects a benefit for the intervention group compared to the control group. If one study measured the respective outcome measure, the results from this study are described. An SMD of < 0.3 is considered as a slight effect of the intervention; 0.3-0.5 as a moderate effect and > 0.5 as a large effect. **e** 1 = down-grading for inconsistency; 2 = down-grading for inaccuracy; 3 = down-grading for inconsistency and inaccuracy; 4 = down-grading for limitations in the study design and method and inconsistency; 5 = down-grading for limitations in study design and method and inaccuracy; 6 = down-grading for limitations in study design and method, inconsistency and inaccuracy. **f** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.

From evidence to recommendation

When formulating the direction and strength of the recommendation for exercise therapy for indication 1, the guideline panel considered the following.

- The guideline panel has no preference regarding the intensity of exercise therapy because usable estimated effects for this are lacking. That is why the guideline panel determined the minimum intensity of muscle strength training and aerobic training based on the ACSM guidelines.
- How much patients value a certain intensity of exercise therapy and which intensity they prefer will likely differ from patient to patient. The guideline panel estimates that most patients will have a positive view of the proposed minimum intensity of the exercise therapy, because optimal treatment results can be achieved with that intensity in accordance with the training principles.
- The guideline panel deems implementing exercise therapy with a minimum intensity in daily practice to be acceptable and feasible, because this intensity is viewed as the most indicated treatment intensity.

Sources

1. Bostrom C, Harms-Ringdahl K, Karreskog H, Nordemar R. Effects of static and dynamic shoulder rotator exercises in women with rheumatoid arthritis: a randomised comparison of impairment, disability, handicap, and health. Scand J Rheumatol. 1998;27(4):281-90.
2. Ekdahl C, Andersson SI, Moritz U, Svensson B. Dynamic versus static training in patients with rheumatoid arthritis. Scand J Rheumatol. 1990;19(1):17-26.
3. van den Ende CHM, Hazes JMW, le Cessie S, Mulder WJ, Belfor DG, Breedveld FC, Dijkmans BA. Comparison of high and low intensity training in well controlled rheumatoid arthritis. Results of a randomized clinical trial. Ann Rheum Dis. 1996;55(11):798-805.
4. van den Ende CHM, Breedveld FC, le Cessie S, Dijkmans BAC, de Mug AW, Hazes JMW. Effect of intensive exercise on patients with active rheumatoid arthritis: a randomised clinical trial. Ann Rheum Dis. 2000;59:615-21.
5. American College of Sports Medicine. Guidelines for Exercise Testing and Prescription. 10th Edition. Lippincott William and Wilkins; 2017.

Note 17. Type

Clinical question

Which type of exercise therapy is recommended for patients with RA?

Complete clinical question according to PICO

To answer this clinical question, a joint PICO clinical question was formulated for the frequency, intensity, type and duration of the exercise therapy (see Note 14).

Search strategy

A joint search on the frequency, intensity, type and duration of the exercise therapy was carried out (see Note 14).

Literature found

No randomised controlled studies were found in which the type of exercise therapy was directly investigated (see Note 14). The recommendation for the type of exercise therapy is based on the ACSM guideline.[1]

Description of studies

Not applicable.

Effectiveness and quality of evidence

Not applicable.

From evidence to recommendation

Not applicable.

Sources

1. American College of Sports Medicine. Guidelines for Exercise Testing and Prescription. 10th Edition. Lippincott William and Wilkins; 2017.

Note 18. Duration

Clinical question

Which duration of the exercise therapy is recommended for patients with RA?

Complete clinical question according to PICO

To answer this clinical question, a joint PICO clinical question was formulated for the frequency, intensity, type and duration of the exercise therapy (see Note 14).

Search strategy

A joint search on the frequency, intensity, type and duration of the exercise therapy was carried out (see Note 14).

Literature found

No randomised controlled studies were found in which the duration of the exercise therapy was directly investigated. To be able to formulate a recommendation nevertheless about the duration, a sub-group analysis was performed with the included studies for the clinical question about the effectiveness of exercise therapy in order to determine which duration yields the optimal result (see Note 14).

Description of studies

Of the 19 included studies on the effectiveness of exercise therapy, six studies had a duration of less than three months [1-3, 5, 14, 16], 11 studies a duration of three to six months [4,6,8,9,11-13,15, 17-19] and two studies a duration of more than six months.[7,10] The characteristics of the studies are described in Note 10.

Effectiveness and quality of evidence

The assessment of the study design and execution of the selected articles is included in the appendix to this Note.

Below follows a description of the effectiveness of exercise therapy in relation to its duration and the quality of evidence for each outcome measure. See also the GRADE profiles of exercise therapy of various durations in tables 18.1 through 18.3.

Desired effects

Crucial outcome measures

a) 'Quality of life' outcome measure:
   - The effect and the quality of evidence of exercise therapy for a duration of less than three months (0 studies) and for a duration of more than six months (0 studies) on quality of life is unknown. The effect of exercise therapy for a duration of three to six months (3 studies) on quality of life is large (SMD = 0.77; 95%-CI = -0.08-1.62).
   - The quality of evidence for the 'quality of life' outcome measure for a duration of three to six months was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and small number of patients (inaccuracy).

b) 'Physical functioning' outcome measure:
   - There is a moderate effect (SMD = 0.48; 95%-CI = 0.21-0.74) of exercise therapy for a duration of less than three months (5 studies) on physical functioning. There is also a moderate effect (SMD = 0.42; 95%-CI = 0.14-0.71) of exercise therapy for a duration of three to six months (10 studies) on physical functioning. There is also a moderate effect (SMD = 0.42; 95%-CI = 0.19-0.65) of exercise therapy for a duration of more than six months on physical functioning (2 studies).
   - The quality of evidence for the 'physical functioning' outcome measure for a duration of less than three months was lowered by one level to 'acceptable quality of evidence', given the small number of patients (inaccuracy). The quality of evidence for the 'physical functioning' outcome measure for a duration of three to six months was lowered by one level to 'acceptable quality of evidence', given the contradictory results (inconsistency). The quality of evidence for the 'physical functioning' outcome measure for a duration of more than six months was lowered by one level to 'acceptable quality of evidence', given the small number of patients (inaccuracy).

c) 'Fatigue' outcome measure:
   - The effect and the quality of evidence of exercise therapy for a duration of less than three months, three to six months and more than six months on fatigue is unknown (0 studies).

d) 'Pain' outcome measure:
   - The effectiveness of exercise therapy for a duration of less than three months (SMD unavailable) and a duration of more than six months (0 studies) on pain is unknown. There is a large effect (SMD = 0.82; 95%-CI = -0.45-1.19) of exercise therapy for a duration of three to six months on pain (2 studies).
   - The quality of evidence for the 'pain' outcome measure for a duration of less than three months was lowered by two levels to 'very low quality of evidence', given the limitations of the study design and execution, contradictory results (inconsistency) and small number of patients (inaccuracy). The quality of evidence for the 'pain' outcome measure for a duration of three to six months was lowered by one level to 'acceptable quality of evidence', given the small number of patients (inaccuracy).

Important outcome measures

a) 'Aerobic capacity' outcome measure:
   - There is a moderate effect (SMD = 0.46; 95%-CI = 0.06-0.86) of exercise therapy for a duration of less than three months (3 studies) on aerobic capacity. There is also a moderate effect (SMD = 0.49; 95%-CI = 0.23-0.75) of exercise therapy for a duration of three to six months (6 studies) on physical functioning. The effect of exercise therapy for a duration of more than six months on aerobic capacity is unknown (0 studies).
   - The quality of evidence for the 'aerobic capacity' outcome measure for a duration of less than three months was lowered by one level to 'acceptable quality of evidence', given the small number of patients (inaccuracy). The quality of evidence for the 'aerobic capacity' outcome measure for a duration of three to six months was lowered by one level to 'acceptable quality of evidence', given the small number of patients (inaccuracy).

b) 'Muscle strength' outcome measure:
   - There is a moderate effect (SMD = 0.48; 95%-CI = 0.21-0.74) of exercise therapy for a duration of less than three months (5 studies) on 'muscle strength'. There is also a moderate effect (SMD = 0.42; 95%-CI = 0.14-0.71) of exercise therapy for a duration of three to six months (10 studies) on 'muscle strength'. There is also a moderate effect (SMD = 0.42; 95%-CI = 0.19-0.65) of exercise therapy for a duration of more than six months on 'muscle strength' (2 studies).
   - The quality of evidence for the 'muscle strength' outcome measure for a duration of less than three months was lowered by one level to 'acceptable quality of evidence', given the small number of patients (inaccuracy). The quality of evidence for the 'muscle strength' outcome measure for a duration of three to six months was lowered by one level to 'acceptable quality of evidence', given the small number of patients (inaccuracy). The quality of evidence for the'muscle strength' outcome measure for a duration of more than six months was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and small number of patients (inaccuracy).

c) 'Range of motion' outcome measure:
   - The effectiveness of exercise therapy for a duration of less than three months on 'range of motion' is unknown (0 studies). There is a large effect (SMD = 0.59; 95%-CI = 0.17-1.01) of exercise therapy for a duration of three to six months (2 studies) on 'range of motion'.
   - The effectiveness of exercise therapy for a duration of more than six months on 'range of motion' is unknown (0 studies).
   - The quality of evidence for the 'range of motion' outcome measure for a duration of three to six months was lowered by one level to 'acceptable quality of evidence', given the small number of patients (inaccuracy).

d) 'Work productivity' outcome measure:
   - The effectiveness of exercise therapy for a duration of less than three months and a duration of three to six months or for a duration of more than six months on 'work productivity' is unknown (0 studies).

Undesirable effects

a) 'Disease activity' outcome measure:
   - There is a slight effect (SMD = 0.24; 95%-CI = -0.57-1.06) of exercise therapy for a duration of less than three months (4 studies) on 'disease activity'. There is also a moderate effect (SMD = 0.43; 95%-CI = -0.01-0.87) of exercise therapy for a duration of three to six months (3 studies) on 'disease activity'. There is a slight effect (SMD = 0.03; 95%-CI = -0.46-0.52) of exercise therapy for a duration of more than six months (2 studies) on 'disease activity'.

- The quality of evidence for the 'disease activity' outcome measure for a duration of less than three months was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and small number of patients (inaccuracy). The quality of evidence for the 'disease activity' outcome measure for a duration of three to six months was lowered by two levels to 'low quality of evidence', given the limitations of the study design and method and the small number of patients (inaccuracy). The quality of evidence for the 'disease activity' outcome measure for a duration of more than six months was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and small number of patients (inaccuracy).

b) 'Radiological damage' outcome measure:
   - The effect of exercise therapy for a duration of less than three months and for a duration of three to six months on 'radiological damage' is unknown (0 studies). There is a slight effect (SMD = 0.09; 95%-CI = -0.14-0.31) of exercise therapy for a duration of more than six months on 'radiological damage' (2 studies).
   - The quality of evidence for the 'radiological damage' outcome measure for a duration of more than six months was lowered by one level to 'acceptable quality of evidence', given the small number of patients (inaccuracy).

Table 18.1. GRADE profile of exercise therapy for a duration of less than three months.

	Number of studies	GRADE+					Number of patients		Estimated effect	Quality of evidence
		Limitations in study design and execution[a]	Inconsistency[b]	Indirectness	Inaccuracy[c]	Other	Exercise therapy	Control	Standardized mean difference (95%-CI)[d]	very low / low / acceptable / high[e]
Desired effects	**Crucial outcome measures**									
	Quality of life									
	n = 1	low	unknown	no	yes, *n* = 48	no	25	23	no significant effect	low (3)
	Physical functioning									
	n = 5	moderate	no, I^2 = 0%	no	yes, *n* = 230	no	119	111	0,11 (0,21 to 0,74)	acceptable (2)
	Fatigue									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Pain									
	n = 1	high	unknown	no	yes, *n* = 93	no	47	46	no significant effect	very low (6)
	Important outcome measures									
	Aerobic capacity									
	n = 3	moderate	no, I^2 = 0%	no	yes, *n* = 102	no	55	47	0,46 (0,06 to 0,86)	acceptable (2)
	Muscle strength									
	n = 12	moderate	yes, I^2 = 95%	no	yes, *n* = 171	no	84	87	0,99 (-0,60 to 2,58)	low (3)
	Range of motion									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Work productivity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Undesirable effects[f]	**Disease activity**									
	n = 4	moderate	yes, I^2 = 80%	no	yes, *n* = 171	no	84	87	0,24 (-0,57 to 1,06)	low (3)
	Radiological damage									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

n/a: not applicable. **a** Limitations in study design and execution were low in the case of random assignment + allocation concealed + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading took place with a high score. **b** Down-grading took place with I2 > 40%. **c** Down-grading took place in the event of a dichotomous outcome measure with n < 300 and in the case of a continuous outcome measure with *n* < 400. **d** A positive standardised mean difference (SMD) reflects a benefit for the intervention group compared to the control group. If one study measured the respective outcome measure, the results from this study are described. An SMD of < 0.3 is considered as a slight effect of the intervention; 0.3-0.5 as a moderate effect and > 0.5 as a large effect. **e** 1 = down-grading for inconsistency; 2 = down-grading for inaccuracy; 3 = down-grading for inconsistency and inaccuracy; 4 = down-grading for limitations in the study design and method and inconsistency; 5 = down-grading for limitations in study design and method and inaccuracy; 6 = down-grading for limitations in study design and method, inconsistency and inaccuracy. **f** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.

Table 18.2. GRADE profile of exercise therapy for a duration of three to six months.

	Number of studies	GRADE+					Number of patients		Estimated effect	Quality of evidence
		Limitations in study design and execution[a]	Inconsistency[b]	Indirectness	Inaccuracy[c]	Other	Exercise therapy	Control	Standardized mean difference (95%-CI)[d]	very low / low / acceptable / high[e]
Desired effects	**Crucial outcome measures**									
	Quality of life									
	n = 3	moderate	yes, I^2 = 86%	no	yes, *n* = 145	no	71	74	0,77 (-0,08 to 1,62)	low (3)
	Physical functioning									
	n = 10	moderate	yes, I^2 = 52%	no	no, *n* = 453	no	233	220	0,42 (0,14 to 0,71)	acceptable (1)
	Fatigue									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Pain									
	n = 2	moderate	no, I^2 = 0%	no	yes, *n* = 126	no	67	59	0,82 (95%-BI:-0,45 to 1,19)	acceptable (2)
	Important outcome measures									
	Aerobe capaciteit									
	n = 6	moderate	no, I^2 = 0%	no	yes, *n* = 233	no	119	114	0,49 (0,23 to 0,75)	acceptable (2)
	Muscle strength									
	n = 7	moderate	no, I^2 = 0%	no	yes, *n* = 219	no	110	109	0,44 (0,17 to 0,72)	acceptable (2)
	Range of motion									
	n = 2	high	no, I^2 = 0%	no	yes, *n* = 93	no	45	48	0,59 (0,17 to 1,01)	low (5)
	Work productivity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Undesirable effects[f]	**Disease activity**									
	n = 3	high	no, I^2 = 0%	no	yes, *n* = 84	no	41	43	0,43 (-0,01 to 0,87)	low (5)
	Radiological damage									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

n/a: not applicable. **a** Limitations in study design and execution were low in the case of random assignment + allocation concealed + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading took place with a high score. **b** Down-grading took place with I2 > 40%. **c** Down-grading took place in the event of a dichotomous outcome measure with n < 300 and in the case of a continuous outcome measure with *n* < 400. **d** A positive standardised mean difference (SMD) reflects a benefit for the intervention group compared to the control group. If one study measured the respective outcome measure, the results from this study are described. An SMD of < 0.3 is considered as a slight effect of the intervention; 0.3-0.5 as a moderate effect and > 0.5 as a large effect. **e** 1 = down-grading for inconsistency; 2 = down-grading for inaccuracy; 3 = down-grading for inconsistency and inaccuracy; 4 = down-grading for limitations in the study design and method and inconsistency; 5 = down-grading for limitations in study design and method and inaccuracy; 6 = down-grading for limitations in study design and method, inconsistency and inaccuracy. **f** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.

Table 18.3. GRADE profile of exercise therapy for a duration of more than six months.

	Number of studies	GRADE+					Number of patients		Estimated effect	Quality of evidence
		Limitations in study design and execution[a]	Inconsistency[b]	Indirectness	Inaccuracy[c]	Other	Exercise therapy	Control	Standardized mean difference (95%-CI)[d]	very low / low / acceptable / high[e]
Desired effects	**Crucial outcome measures**									
	Quality of life									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Physical functioning									
	n = 2	moderate	no, I^2 = 0%	no	yes, *n* = 305	no	147	158	0,42 (0,19 to 0,65)	acceptable (2)
	Fatigue									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Pain									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Important outcome measures									
	Aerobic capacity									
	n = 1	low	onbekend	no	yes, *n* = 281	no	136	145	A significant difference was found in favour of exercise therapy	low (3)
	Muscle strength									
	n = 2	moderate	yes, I^2 = 77%	no	yes, *n* = 305	no	147	158	0,73 (-0,22 to 1,68)	low (3)
	Range of motion									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Work productivity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Undesirable effects[f]	**Disease activity**									
	n = 2	moderate	yes, I^2 = 43%	no	yes, *n* = 305	no	147	158	0,03 (-0,46 to 0,52)	low (3)
	Radiological damage									
	n = 2	moderate	no, I^2 = 0%	no	yes, *n* = 305	no	147	158	0,09 (-0,14 to 0,31)	acceptable (2)

n/a: not applicable. **a** Limitations in study design and execution were low in the case of random assignment + allocation concealed + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading took place with a high score. **b** Down-grading took place with I2 > 40%. **c** Down-grading took place in the event of a dichotomous outcome measure with n < 300 and in the case of a continuous outcome measure with *n* < 400. **d** A positive standardised mean difference (SMD) reflects a benefit for the intervention group compared to the control group. If one study measured the respective outcome measure, the results from this study are described. An SMD of < 0.3 is considered as a slight effect of the intervention; 0.3-0.5 as a moderate effect and > 0.5 as a large effect. **e** 1 = down-grading for inconsistency; 2 = down-grading for inaccuracy; 3 = down-grading for inconsistency and inaccuracy; 4 = down-grading for limitations in the study design and method and inconsistency; 5 = down-grading for limitations in study design and method and inaccuracy; 6 = down-grading for limitations in study design and method, inconsistency and inaccuracy. **f** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.

From evidence to recommendation

When formulating the direction and strength of the recommendation for exercise therapy for indication 1, the guideline panel considered the following.

- Based on the magnitude of the estimated effects and the quality of evidence, the guideline panel believes that exercise therapy for a duration of three to six months is preferable. The guideline panel adds that the aim is to supplement the treatment period with one or several follow-up sessions toward the end or after completion of the treatment period in order to facilitate therapy adherence and to encourage the patient to continue exercising and be active independently during and after the treatment period.
- How much patients value a certain duration of exercise therapy and which duration they prefer will likely differ from patient to patient. The guideline panel estimates that the majority of patients will have a positive view of exercise therapy for a duration of three to six months.
- The potential costs for the patient are higher for a duration of three to six months than for a duration of less than three months. However, the guideline panel believes that this cost aspect is compensated for by the fact that a longer time span yields a better effect.
- The guideline panel deems implementing exercise therapy for a duration of three to six months in daily practice to be acceptable and feasible, because this duration is viewed as the most indicated option.

Sources

1. Baillet A, Payraud E, Niderprim VA, Nissen MJ, Allenet B, François P, Grange L, Casez P, Juvin R, Gaudin P. A dynamic exercise programme to improve patients' disability in rheumatoid arthritis: a prospective randomized controlled trial. Rheumatology (Oxford). 2009 Apr;48(4):410-5.
2. Baslund B, Lyngberg K, Andersen V, Halkjaer Kristensen J, Hansen M, Klokker M, et al. Effect of 8 wk of bicycle training on the immune system of patients with rheumatoid arthritis. Journal of Applied Physiology 1993;75:1691–5.
3. Bearne LM, Scott DL, Hurley MV. Exercise can reverse quadriceps sensorimotor dysfunction that is associated with rheumatoid arthritis without exacerbating disease activity. Rheumatology (Oxford). 2002 Feb;41(2):157-66.
4. Bilberg A, Ahlmén M, Mannerkorpi K. Moderately intensive exercise in a temperate pool for patients with rheumatoid arthritis: a randomized controlled study. Rheumatology (Oxford). 2005 Apr;44(4):502-8.
5. Breedland I, van Scheppingen C, Leijsma M, Verheij-Jansen NP, van Weert E. Effects of a group-based exercise and educational program on physical performance and disease self-management in rheumatoid arthritis: a randomized controlled study. Phys Ther. 2011 Jun;91(6):879-93.
6. da Silva KN, Teixeira LE, Imoto AM, Atallah AN, Peccin MS, Trevisani VF. Effectiveness of sensorimotor training in patients with rheumatoid arthritis: a randomized controlled trial. Rheumatol Int. 2013 Sep;33(9):2269-75.
7. de Jong Z, Munneke M, Zwinderman AH, Kroon HM, Jansen A, Ronday KH, et al. Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. Arthritis and Rheumatism 2003;48(9):2415–24.
8. Flint-Wagner HG, Lisse J, Lohman TG, Going SB, Guido T, Cussler E, Gates D, Yocum DE. Assessment of a sixteen-week training program on strength, pain, and function in rheumatoid arthritis patients. J Clin Rheumatol. 2009 Jun;15(4):165-71,
9. Häkkinen A, Häkkinen K, Hannonen P. Effects of strength training on neuromuscular function and disease activity in patients with recent-onset inflammatory arthritis. Scand J Rheumatol. 1994;23(5):237-42.
10. Hansen TM, Hansen G, Langgaard AM, Rasmussen JO. Longterm physical training in rheumatoid arthritis. A randomized trial with different training programs and blinded observers. Scandinavian Journal of Rheumatology 1993;22(3):107–12.
11. Harkcom TM, Lampman RM, Banwell BF, Castor CW. Therapeutic value of graded aerobic exercise training in rheumatoid arthritis. Arthritis and Rheumatism 1985;28(1):32–9.
12. Lemmey AB, Marcora SM, Chester K, Wilson S, Casanova F, Maddison PJ. Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial. Arthritis Rheum. 2009 Dec 15;61(12):1726-34.
13. Lyngberg KK, Harreby M, Bentzen H, Frost B. Elderly rheumatoid arthritis on steroid treatment tolerate physical training without an increase in disease activity. Archives of Physical Medicine and Rehabilitation 1994;75:1189–95.
14. McMeeken J, Stillman B, Story I, Kent P, Smith J. The effects of knee extensor and flexor muscle training on the timed-up-and-go test in individuals with rheumatoid arthritis. Physiother Res Int. 1999;4(1):55-67.
15. Minor MA, Hewett JE, Webel RR, Anderson SK, Kay DR. Efficacy of physical conditioning exercise in patients with rheumatoid arthritis and osteoarthritis. Arthritis and Rheumatism 1989;32(11):1396–405.

16. Sanford-Smith S, Mackay-Lyons M, Nunes-Clement S. Therapeutic benefit of aquaerobics for individuals with rheumatoid arthritis. Physiotherapy Canada 1998;Winter:40–6.
17. Siqueira US, Orsini Valente LG, de Mello MT, Szejnfeld VL, Pinheiro MM. Effectiveness of Aquatic Exercises in Women With Rheumatoid Arthritis: A Randomized, Controlled, 16-Week Intervention-The HydRA Trial. Am J Phys Med Rehabil. 2017 Mar;96(3):167-175.
18. Strasser B, Leeb G, Strehblow C, Schobersberger W, Haber P, Cauza E. The effects of strength and endurance training in patients with rheumatoid arthritis. Clin Rheumatol. 2011 May;30(5):623-32.
19. Van den Ende CHM, Hazes JMW, Le Cessie S, Mulder WJ, Belfor DG, Breedveld FC, Dijkmans BA. Comparison of high and low intensity training in well controlled rheumatoid arthritis. Results of a randomized clinical trial. Annals of the Rheumatic Diseases 1996;55(11):798–805.

Note 19. General factors

Clinical question

Which general factors does the exercise therapy for patients with RA have to meet?
This clinical question was answered by describing the general factors which exercise therapy for patients with RA must meet, based on the ACSM guideline.1 Reviews were carried out to determine the effectiveness of exercise therapy in patients with hand problems and the effectiveness of exercise therapy in water.

Complete clinical question according to PICO

To answer this clinical question, a joint PICO clinical question was formulated for the frequency, intensity, type and duration of the exercise therapy (see Note 14).

Search strategy
A joint search on the frequency, intensity, type and duration of the exercise therapy was carried out (see Note 14).

Literature found
The literature search yielded 1837 references. Four randomised controlled studies met the inclusion criteria for answering the clinical question regarding the effectiveness of exercise therapy in patients with hand problems [2-5], and two studies met the inclusion criteria regarding the effectiveness of exercise therapy on land versus exercise therapy in water. [6-7]

Exercise therapy for patients with hand problems

Description of studies
Four studies investigated the effectiveness of specific hand exercises [2-5], with a comparison being made between isotonic and isometric hand exercises in one study.[2]

Effectiveness and quality of evidence
The assessment of the study design and execution of the selected articles is included in the appendix to this Note.

Below follows a description of the effectiveness of hand exercises as well as the quality of evidence for each outcome measure. See also the GRADE profile of exercise therapy on land versus exercise therapy in water in table 19.2.

Desired effects

Crucial outcome measures

a) 'Quality of life' outcome measure (1 study):
   - The effect of hand exercises on quality of life is unknown (SMD unavailable).
   - The quality of evidence for the 'quality of life' outcome measure is high; no down-grading took place.

b) 'Physical functioning' outcome measure (3 studies):
   - There is a large effect (SMD = 0.61; 95%-CI = 0.04-1.18) of hand exercises on physical functioning.
   - The quality of evidence for the 'physical functioning' outcome measure was lowered by two levels to 'low quality of evidence', given the limitations of the study design and execution and the contradictory results (inconsistency).

c) 'Fatigue' outcome measure (0 studies):
   - The effect and the quality of evidence of hand exercises on fatigue is unknown.

d) 'Pain' outcome measure (1 study):
   - The effect of hand exercises on pain is unknown (SMD unavailable).
   - The quality of evidence for the 'pain' outcome measure is high; no down-grading took place.

Important outcome measures

a) 'Aerobic capacity' outcome measure (0 studies):
   - The effect and the quality of evidence of hand exercises on aerobic capacity is unknown.

b) 'Muscle strength' outcome measure (2 studies):
   - There is a moderate effect (SMD = 0.34; 95%-CI = -0.25-0.93) of hand exercises on muscle strength.
   - The quality of evidence for the 'muscle strength' outcome measure was lowered by one level to 'acceptable quality of evidence', given the contradictory results (inconsistency).

c) 'Range of motion' outcome measure (2 studies):
   - There is a slight effect (SMD = 0.09; 95%-CI = -0.08-0.26) of hand exercises on range of motion.
   - The quality of evidence for the 'range of motion' outcome measure is high.

d) 'Work productivity' outcome measure (1 study):
   - The effect of hand exercises on work productivity is unknown (SMD unavailable).

Undesirable effects

a) 'Disease activity' outcome measure (1 study):
   - The effect of hand exercises on disease activity is unknown (SMD unavailable).

b) 'Radiological damage' outcome measure (0 studies):
   - The effect of hand exercises on radiological damage is unknown.

Table 19.1. GRADE profile of hand exercises.

	Number of studies	GRADE+					Number of patients		Estimated effect	Quality of evidence
		Limitations in study design and execution[a]	Inconsistency[b]	Indirectness	Inaccuracy[c]	Other	Exercise therapy	Control	Standardized mean difference (95%-CI)[d]	very low / low / acceptable / high[e]
Desired effects	**Crucial outcome measures**									
	Quality of life									
	n = 1	low	unknown	unknown	unknown	unknown	246	242	no significant effect found compared to usual care	high
	Physical functioning									
	n = 3	high	yes, I^2 = 66%	no	no, *n* = 548	no	277	271	0,61 (0,04 to 1,18)	low (4)
	Fatigue									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Pain									
	n = 1	low	unknown	unknown	unknown	unknown	246	242	no significant effect found compared to usual care	high
	Important outcome measures									
	Aerobic capacity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Muscle strength									
	n = 2	moderate	yes, I^2 = 72%	no	no, *n* = 531	no	267	264	0,34 (-0,25 to 0,93)	acceptable (1)
	Range of motion									
	n = 2	moderate	no, I^2 = 0%	no	no, *n* = 531	no	267	264	0,09 (-0,08 to 0,26)	high
	Work productivity									
	n = 1	low	unknown	unknown	unknown	unknown	246	242	a significant effect was found in favour of hand exercises	high
Undesirable effects[f]	**Disease activity**									
	n = 1	low	unknown	unknown	unknown	unknown	246	242	no significant effect compared to usual care	high
	Radiological damage									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

n/a: not applicable. **a** Limitations in study design and execution were low in the case of random assignment + allocation concealed + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading took place with a high score. **b** Down-grading took place with I2 > 40%. **c** Down-grading took place in the event of a dichotomous outcome measure with n < 300 and in the case of a continuous outcome measure with *n* < 400. **d** A positive standardised mean difference (SMD) reflects a benefit for the intervention group compared to the control group. If one study measured the respective outcome measure, the results from this study are described. An SMD of < 0.3 is considered as a slight effect of the intervention; 0.3-0.5 as a moderate effect and > 0.5 as a large effect. **e** 1 = down-grading for inconsistency; 2 = down-grading for inaccuracy; 3 = down-grading for inconsistency and inaccuracy; 4 = down-grading for limitations in the study design and method and inconsistency; 5 = down-grading for limitations in study design and method and inaccuracy; 6 = down-grading for limitations in study design and method, inconsistency and inaccuracy. **f** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.

From evidence to recommendation

When formulating the recommendation (direction and strength) for exercise therapy for indication 1, the following items were additionally considered.

- The desired effects of hand therapy on physical functioning are present, while the undesirable effects (such as increased disease activity) appear to be rare. Even though the estimated effects are of limited magnitude and there is uncertainty about the probability of the estimated effects, the guideline panel believes that the desired effects outweigh the undesirable effects.
- How much patients value hand exercises will likely differ from patient to patient. The guideline panel estimates that the majority of patients with hand problems will have a positive view of hand exercises.
- The guideline panel deems implementing hand exercises in daily practice to be acceptable and feasible.

Exercise therapy on land versus exercise therapy in water

Description of studies

Two studies compared exercise therapy on land versus exercise therapy in water.[6,7]

Effectiveness and quality of evidence

The assessment of the study design and execution of the selected articles is included in the appendix to this Note.

Below follows a description of the effectiveness of exercise therapy on land versus exercise therapy in water as well as the quality of evidence for each outcome measure.

Desired effects

Crucial outcome measures

a) 'Quality of life' outcome measure (0 studies):
   - The effect and the quality of evidence of exercise therapy on land versus exercise therapy in water on quality of life is unknown.

b) 'Physical functioning' outcome measure (2 studies):
   - The effect of exercise therapy on land versus exercise therapy in water on physical functioning is unknown (SMD unavailable).
   - The quality of evidence for the 'physical functioning' outcome measure was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and the small number of patients (inaccuracy).

c) 'Fatigue' outcome measure (0 studies):
   - The effect and the quality of evidence of exercise therapy on land versus exercise therapy in water on fatigue is unknown.

d) 'Pain' outcome measure (1 study):
   - The effect and the quality of evidence of exercise therapy on land versus exercise therapy in water on pain is unknown (0 studies).

Important outcome measures

a) 'Aerobic capacity' outcome measure (1 study):
   - The effect and the quality of evidence of exercise therapy in water versus exercise therapy on land on aerobic capacity is unknown (SMD unavailable).

b) 'Muscle strength' outcome measure (2 studies):
   - The effect and the quality of evidence of exercise therapy in water versus exercise therapy on land on muscle strength is unknown (SMD unavailable).

c) 'Range of motion' outcome measure (0 studies):
   - The effect and the quality of evidence of exercise therapy in water versus exercise therapy on land on range of motion is unknown.

d) 'Work productivity' outcome measure (0 studies):
   - The effect and the quality of evidence of exercise therapy in water versus exercise therapy on land on work productivity is unknown.

Undesirable effects

a) 'Disease activity' outcome measure (2 studies):
   - The effect and the quality of evidence of exercise therapy in water versus exercise therapy on land on disease activity is unknown (SMD unavailable).

b) 'Radiological damage' outcome measure (0 studies):
   - The effect and the quality of evidence of exercise therapy in water versus exercise therapy on land on work productivity is unknown.

Table 19.2. GRADE profile of exercise therapy on land versus exercise therapy in water.

	Number of studies	GRADE+					Number of patients		Estimated effect	Quality of evidence
		Limitations in study design and execution[a]	Inconsistency[b]	Indirectness	Inaccuracy[c]	Other	Exercise therapy	Control	Standardized mean difference (95%-CI)[d]	very low / low / acceptable / high[e]
Desired effects	**Crucial outcome measures**									
	Quality of life									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Physical functioning									
	n = 2	moderate	unknown	no	yes, *n* = 132	no	71	61	no significant difference	low (3)
	Fatigue									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Pain									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Important outcome measures									
	Aerobic capacity									
	n = 1	moderate	unknown	no	yes, *n* = 66	no	33	33	no significant difference	low (3)
	Muscle strength									
	n = 2	moderate	unknown	no	yes, *n* = 132	no	71	61	no significant difference	low (3)
	Range of motion									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Work productivity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Undesirable effects[f]	**Disease activity**									
	n = 2	moderate	unknown	no	yes, *n* = 132	no	71	61	no significant difference	low (3)
	Radiological damage									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

n/a: not applicable. **a** Limitations in study design and execution were low in the case of random assignment + allocation concealed + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading took place with a high score. **b** Down-grading took place with I2 > 40%. **c** Down-grading took place in the event of a dichotomous outcome measure with n < 300 and in the case of a continuous outcome measure with *n* < 400. **d** A positive standardised mean difference (SMD) reflects a benefit for the intervention group compared to the control group. If one study measured the respective outcome measure, the results from this study are described. An SMD of < 0.3 is considered as a slight effect of the intervention; 0.3-0.5 as a moderate effect and > 0.5 as a large effect. **e** 1 = down-grading for inconsistency; 2 = down-grading for inaccuracy; 3 = down-grading for inconsistency and inaccuracy; 4 = down-grading for limitations in the study design and method and inconsistency; 5 = down-grading for limitations in study design and method and inaccuracy; 6 = down-grading for limitations in study design and method, inconsistency and inaccuracy. **f** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.

From evidence to recommendation

When formulating the recommendation (direction and strength) for exercise therapy for indication 1, additional items were considered.

The desired effects of exercise therapy on land versus exercise therapy in water are not demonstrated.

- Whether the patient prefers exercise therapy on land or exercise therapy in water will likely differ from patient to patient. The guideline panel estimates that the majority of patients will have a positive view of exercise therapy in water.
- The guideline panel estimates that patients with severe symptoms in the initial phase of treatment will have a positive view of exercise therapy in water.
- The guideline panel deems implementing exercise therapy in water for patients with severe symptoms in the initial phase of treatment in daily practice to be acceptable and feasible.

Sources

1. American College of Sports Medicine. Guidelines for Exercise Testing and Prescription. 10th Edition. Lippincott William and Wilkins; 2017.
2. Dogu B, Sirzai H, Yilmaz F, Polat B, Kuran B. Effects of isotonic and isometric hand exercises on pain, hand functions, dexterity and quality of life in women with rheumatoid arthritis. Rheumatol Int. 2013;33(10):2625-30,
3. Cima SR, Barone A, Porto JM, de Abreu DC. Strengthening exercises to improve hand strength and functionality in rheumatoid arthritis with hand deformities: a randomized, controlled trial. Rheumatol Int. 2013;33(3):725-32.
4. Lamb SE, Williamson EM, Heine PJ, Adams J, Dosanjh S, Dritsaki M, et al. Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet. 2015;385(9966):421-9.
5. O'Brien AV, Jones P, Mullis R, Mulherin D, Dziedzic K. Conservative hand therapy treatments in rheumatoid arthritis-a randomized controlled trial. Rheumatology (Oxford). 2006;45(5):577-83.
6. Minor MA, Hewett JE, Webel RR, Anderson SK, Kay DR. Efficacy of physical conditioning exercise in patients with rheumatoid arthritis and osteoarthritis. Arthritis and Rheumatism 1989;32(11):1396-405.
7. Siqueira US, Orsini Valente LG, de Mello MT, Szejnfeld VL, Pinheiro MM. Effectiveness of aquatic exercises in women with rheumatoid arthritis: a randomized, controlled, 16-week intervention-the HydRA Trial. Am J Phys Med Rehabil. 2017 Mar;96(3):167-175.

Note 20. Modification of exercise therapy due to comorbidity

Clinical question

Which modifications to the exercise therapy are recommended for patients with RA if they have one or more forms of comorbidity that affect their physical functioning?

The following literature was used to answer the clinical question:

Sources

1. Dekker J, de Rooij M, van der Leeden M. Exercise and comorbidity: the i3-S strategy for developing comorbidity-related adaptations to exercise therapy. Disabil Rehabil. 2016;38(9):905-9.
2. de Rooij M, van der Leeden M, Avezaat E, Häkkinen A, Klaver R, Maas T, et al. Development of comorbidity-adapted exercise protocols for patients with knee osteoarthritis. Clin Interv Aging. 2014 May 14;9:829-42.
3. van der Leeden M, Huijsmans RJ, Geleijn E, de Rooij M, Konings IR, Buffart LM, et al. Tailoring exercise interventions to comorbidities and treatment-induced adverse effects in patients with early stage breast cancer undergoing chemotherapy: a framework to support clinical decisions. Disabil Rehabil. 2018 Feb;40(4):486-96.

Note 21. Non-exercise therapy interventions

Clinical question

Are non-exercise therapy interventions, either as an addition to the exercise therapy intervention or not, recommended for patients with RA?

Complete clinical question according to PICO

Which non-exercise therapy interventions (I), compared to no exercise therapy (C), are and which are not recommended for patients with RA (P) – either as an addition to the exercise therapy intervention or not – to improve their quality of life, physical functioning, pain, fatigue, aerobic capacity, muscle strength, range of motion, disease activity, radiological damage and work productivity (O)?

Search strategy

On March 3, 2017, the KNGF conducted a search on summaries of the literature (i.e. systematic review) and randomised controlled studies on non-exercise therapy interventions in patients with RA. The search terms for exercise therapy are included in the attachment to this Note. The selection criteria for inclusion are shown in table 21.1.

Table 21.1. Selection criteria for systematic review of non-exercise therapy interventions.

Type of study	RCT
Type of patient	Adults diagnosed with rheumatoid arthritis based on the ARA or ACR/EULAR classification criteria
Type of intervention	any form of: • passive mobilisation • massage • thermotherapy • administration of electrostimulation • administration of electrostimulation using TENS • administration of electromagnetic energy • administration of mechanical energy (ultrasound) • medical taping • dry needling
Type of comparison	no intervention or usual care
Type of outcome	crucial outcome measures: quality of life, physical functioning, pain*, fatigue crucial outcome measures: aerobic capacity, muscle strength, range of motion, disease activity*, radiological damage*, work productivity
Type of timeline	immediately after the intervention

** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.*

Literature found

The literature search yielded 82 references for low-level laser therapy, 82 references for ultrasound, 82 references for electrostimulation, 82 references for transcutaneous electrical nerve stimulation (TENS), 65 references for massage, 179 references for thermotherapy, 38 references for medical taping and 100 references for passive mobilisation. After screening of the title and abstract, seven articles were included for low-level laser therapy [3-5, 7-10], one article for ultrasound [6], one article for electrostimulation [1] and one article for TENS [2]. The flowcharts of the systematic reviews of the non-exercise therapy interventions can be requested from the authors of this guideline. Based on the selection criteria, no articles could be included that investigated the effectiveness of massage, thermotherapy, medical taping and passive mobilisation.

Description of studies

Low-level laser therapy: The duration varied from three days to 10 weeks with a frequency of twice per week to daily.
Electrostimulation: The duration was 10 weeks, with a frequency varying from 1 hour to 3 hours per day.
TENS: The study on TENS had a duration of 20 minutes.
Ultrasound: The duration was three weeks with a frequency of four to five times per week.

Effectiveness and quality of evidence
The assessment of the study design and execution of the selected articles is included in the appendix to this Note.

Below follows a description of the effectiveness of non-exercise therapy interventions as well as the quality of evidence for each outcome measure.

Low-level laser therapy

Desired effects

Crucial outcome measures

a) 'Quality of life' and 'fatigue' outcome measures (0 studies):
   - The effect and the quality of evidence of low-level laser therapy on quality of life and fatigue in patients with RA, compared to no intervention or usual care is unknown.

b) 'Physical functioning' outcome measure (3 studies):
   - The effect of low-level laser therapy on physical functioning in patients with RA compared to no intervention or usual care is low (SMD = 0.20; 95%-CI = -0.14-0.55).
   - The quality of evidence for the 'physical functioning' outcome measure was lowered by two levels to 'low quality of evidence', given the limitations of the study design and execution and the small number of patients (inaccuracy).

c) 'Pain' outcome measure (3 studies):
   - The effect of low-level laser therapy on pain in patients with RA compared to no intervention or usual care is large (SMD = 0.92; 95%-CI = -0.74-2.57).
   - The quality of evidence for the 'pain' outcome measure was lowered by three levels to 'very low quality of evidence', given the limitations of the study design and execution, the contradictory results (inconsistency) and the small number of patients (inaccuracy).

Important outcome measures

a) 'Range of motion' outcome measure (1 study):
   - The effect of low-level laser therapy on range of motion in patients with RA compared to no intervention or usual care is unknown (SMD unavailable).
   - The quality of evidence for the 'range of motion' outcome measure was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and small number of patients (inaccuracy).

b) 'Aerobic capacity', 'muscle strength' and 'work productivity' outcome measures (0 studies):
   - The effect and the quality of evidence of low-level laser therapy on these outcome measures is unknown.

Undesirable effects

a) 'Disease activity' outcome measure (4 studies):
   - The effect of low-level laser therapy on disease activity in patients with RA compared to no intervention or usual care is moderate (SMD = 0.41; 95%-CI = -0.07-0.88).
   - The quality of evidence for the 'disease activity' outcome measure was lowered by three levels to 'very low quality of evidence', given the limitations of the study design and execution, the contradictory results (inconsistency) and the small number of patients (inaccuracy).

b) 'Radiological damage' outcome measure (1 study):
   - The effect of low-level laser therapy on radiological damage in patients with RA compared to no intervention or usual care is unknown (SMD unavailable).
   - The quality of evidence for the 'radiological damage' outcome measure was lowered by three levels to 'very low quality of evidence', given the limitations of the study design and execution, contradictory results (inconsistency) and small number of patients (inaccuracy).

The GRADE profile of low-level laser therapy is shown in table 21.2.

Table 21.2. GRADE profile of low-level laser therapy.

	Number of studies	GRADE+					Number of patients		Estimated effect	Quality of evidence
		Limitations in study design and execution[a]	Inconsistency[b]	Indirectness	Inaccuracy[c]	Other	Exercise therapy	Control	Standardized mean difference (95%-CI)[d]	very low / low / acceptable / high[e]
Desired effects	**Crucial outcome measures**									
	Quality of life									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Physical functioning									
	n = 3	high	no, I^2 = 0%	no	yes, *n* = 139	no	76	63	0,20 (-0,14 to 0,55)	low (5)
	Fatigue									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Pain									
	n = 3	high	yes, I^2 = 92%	no	yes, *n* = 97	no	55	42	0,92 (-0,74 to 2,57)	very low (6)
	Important outcome measures									
	Aerobic capacity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Muscle strength									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Range of motion									
	n = 1	moderate	unknown	no	yes, *n* = 35	no	25	10	no significant difference for ROM compared to control	low (3)
	Work productivity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Undesirable effects[f]	**Disease activity**									
	n = 4	high	yes, I^2 = 42%	no	yes, *n* = 132	no	74	58	0,41 (-0,07 to 0,88)	very low (6)
	Radiological damage									
	n = 1	high	unknown	n.a.	yes, *n* = 40	n.a.	20	20	no significant effect compared to control	very low (6)

n/a: not applicable. **a** Limitations in study design and execution were low in the case of random assignment + allocation concealed + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading took place with a high score. **b** Down-grading took place with I2 > 40%. **c** Down-grading took place in the event of a dichotomous outcome measure with n < 300 and in the case of a continuous outcome measure with *n* < 400. **d** A positive standardised mean difference (SMD) reflects a benefit for the intervention group compared to the control group. If one study measured the respective outcome measure, the results from this study are described. An SMD of < 0.3 is considered as a slight effect of the intervention; 0.3-0.5 as a moderate effect and > 0.5 as a large effect. **e** 1 = down-grading for inconsistency; 2 = down-grading for inaccuracy; 3 = down-grading for inconsistency and inaccuracy; 4 = down-grading for limitations in the study design and method and inconsistency; 5 = down-grading for limitations in study design and method and inaccuracy; 6 = down-grading for limitations in study design and method, inconsistency and inaccuracy. **f** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.

Electrostimulation

Desired effects

Crucial outcome measures

a) 'Quality of life', 'physical functioning', 'fatigue' and 'pain' outcome measures (0 studies):
   - The effect and the quality of evidence of electrostimulation on 'quality of life', 'physical functioning', 'fatigue' and 'pain' in patients with RA is unknown.

Important outcome measures

a) 'Muscle strength' outcome measure (1 study):
   - The effect of electrostimulation on muscle strength in patients with RA compared to no intervention or usual care is unknown (SMD unavailable).
   - The quality of evidence for the 'muscle strength' outcome measure was lowered by three levels to 'very low quality of evidence', given the limitations of the study design and execution, the contradictory results (inconsistency) and the small number of patients (inaccuracy).

b) 'Aerobic capacity', 'range of motion', 'work productivity', 'disease activity' and 'radiological damage' outcome measures (0 studies):
   - The effect and the quality of evidence of electrostimulation on these outcome measures is unknown.

The GRADE profile of electrostimulation is shown in table 21.3.

Table 21.3. GRADE profile of electrostimulation

	Number of studies	GRADE+					Number of patients		Estimated effect	Quality of evidence
		Limitations in study design and execution[a]	Inconsistency[b]	Indirectness	Inaccuracy[c]	Other	Exercise therapy	Control	Standardized mean difference (95%-CI)[d]	very low / low / acceptable / high[e]
Desired effects	**Crucial outcome measures**									
	Quality of life									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Physical functioning									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Fatigue									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Pain									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Important outcome measures									
	Aerobic capacity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Muscle strength									
	n = 1	high	unknown	no	yes, *n* = 18	no	12	6	significantly more improvement on grip strength and pinch strength compared to control	very low (6)
	Range of motion									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Work productivity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Undesirable effects[f]	**Disease activity**									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Radiological damage									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

n/a: not applicable. **a** Limitations in study design and execution were low in the case of random assignment + allocation concealed + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading took place with a high score. **b** Down-grading took place with I2 > 40%. **c** Down-grading took place in the event of a dichotomous outcome measure with n < 300 and in the case of a continuous outcome measure with *n* < 400. **d** A positive standardised mean difference (SMD) reflects a benefit for the intervention group compared to the control group. If one study measured the respective outcome measure, the results from this study are described. An SMD of < 0.3 is considered as a slight effect of the intervention; 0.3-0.5 as a moderate effect and > 0.5 as a large effect. **e** 1 = down-grading for inconsistency; 2 = down-grading for inaccuracy; 3 = down-grading for inconsistency and inaccuracy; 4 = down-grading for limitations in the study design and method and inconsistency; 5 = down-grading for limitations in study design and method and inaccuracy; 6 = down-grading for limitations in study design and method, inconsistency and inaccuracy. **f** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.

Transcutaneous electrical nerve stimulation (TENS)

Desired effects

Crucial outcome measures

a) 'Quality of life' and 'physical functioning' outcome measures (0 studies):
   - The effect and the quality of evidence of TENS on the outcome measures 'quality of life' and 'physical functioning' in patients with RA is unknown.

b) 'Fatigue' outcome measure (1 study):
   - The effect of TENS on 'fatigue' in patients with RA compared to no intervention or usual care is unknown (SMD unavailable).
   - The quality of evidence for the 'fatigue' outcome measure was lowered by three levels to 'very low quality of evidence', given the limitations of the study design and execution, the contradictory results (inconsistency) and the small number of patients (inaccuracy).

c) 'Pain' outcome measure (1 study):
   - The effect of TENS on pain in patients with RA compared to no intervention or usual care is unknown (SMD unavailable).
   - The quality of evidence for the 'pain' outcome measure was lowered by three levels to 'very low quality of evidence', given the limitations of the study design and execution, the contradictory results (inconsistency) and the small number of patients (inaccuracy).

Important outcome measures

a) 'Aerobic capacity', 'muscle strength', 'range of motion', 'work productivity', 'disease activity' and 'radiological damage' outcome measures (0 studies):
   - The effect and the quality of evidence of TENS on these outcome measures is unknown.

The GRADE profile of TENS is shown in table 21.4.

Table 21.4. GRADE profile of TENS.

	Number of studies	GRADE+					Number of patients		Estimated effect	Quality of evidence
		Limitations in study design and execution[a]	Inconsistency[b]	Indirectness	Inaccuracy[c]	Other	Exercise therapy	Control	Standardized mean difference (95%-CI)[d]	very low / low / acceptable / high[e]
Desired effects	**Crucial outcome measures**									
	Quality of life									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Physical functioning									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Fatigue									
	n = 1	high	unknown	no	yes, *n* = 33	no	22	11	No statistical comparison done	very low (6)
	Pain									
	n = 1	high	unknown	no	yes, *n* = 33	no	22	11	TENS and acupuncture TENS both significantly better on pain (VAS) compared to control	very low (6)
	Important outcome measures									
	Aerobic capacity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Muscle strength									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Range of motion									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Work productivity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Undesirable effects[f]	**Disease activity**									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Radiological damage									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

n/a: not applicable. **a** Limitations in study design and execution were low in the case of random assignment + allocation concealed + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading took place with a high score. **b** Down-grading took place with I2 > 40%. **c** Down-grading took place in the event of a dichotomous outcome measure with n < 300 and in the case of a continuous outcome measure with *n* < 400. **d** A positive standardised mean difference (SMD) reflects a benefit for the intervention group compared to the control group. If one study measured the respective outcome measure, the results from this study are described. An SMD of < 0.3 is considered as a slight effect of the intervention; 0.3-0.5 as a moderate effect and > 0.5 as a large effect. **e** 1 = down-grading for inconsistency; 2 = down-grading for inaccuracy; 3 = down-grading for inconsistency and inaccuracy; 4 = down-grading for limitations in the study design and method and inconsistency; 5 = down-grading for limitations in study design and method and inaccuracy; 6 = down-grading for limitations in study design and method, inconsistency and inaccuracy. **f** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.

Ultrasound

Desired effects

Crucial outcome measures

a) 'Quality of life' outcome measure (0 studies):
   - The effect and the quality of evidence of ultrasound on quality of life in patients with RA compared to no intervention or usual care is unknown.

b) 'Physical functioning' outcome measure (1 study):
   - The effect of ultrasound on physical functioning in patients with RA compared to no intervention or usual care is unknown (SMD unavailable).
   - The quality of evidence for the 'physical functioning' outcome measure was lowered by three levels to 'very low quality of evidence', given the limitations of the study design and execution, the contradictory results (inconsistency) and the small number of patients (inaccuracy).

c) 'Pain' outcome measure (1 study):
   - The effect of ultrasound on pain in patients with RA compared to no intervention or usual care is unknown (SMD unavailable).
   - The quality of evidence for the 'pain' outcome measure was lowered by three levels to 'very low quality of evidence', given the limitations of the study design and execution, the contradictory results (inconsistency) and the small number of patients (inaccuracy).

Important outcome measures

a) 'Muscle strength' outcome measure (1 study):
   - The effect of ultrasound on muscle strength in patients with RA compared to no intervention or usual care is unknown (SMD unavailable).
   - The quality of evidence for the 'muscle strength' outcome measure was lowered by three levels to 'very low quality of evidence', given the limitations of the study design and execution, the contradictory results (inconsistency) and the small number of patients (inaccuracy).

b) 'Range of motion' outcome measure (1 study):
   - The effect of ultrasound on range of motion in patients with RA compared to no intervention or usual care is unknown (SMD unavailable).
   - The quality of evidence for the 'range of motion' outcome measure was lowered by three levels to 'very low quality of evidence', given the limitations of the study design and execution, the contradictory results (inconsistency) and the small number of patients (inaccuracy).

c) 'Aerobic capacity 'work productivity', 'disease activity' and 'radiological damage' outcome measures (0 studies):
   - The effect and the quality of evidence of ultrasound on these outcome measures is unknown.

The GRADE profile of mechanical energy (ultrasound) is shown in table 21.5.

Table 21.5. GRADE profile of mechanical energy (ultrasound).

	Number of studies	GRADE+					Number of patients		Estimated effect	Quality of evidence
		Limitations in study design and execution[a]	Inconsistency[b]	Indirectness	Inaccuracy[c]	Other	Exercise therapy	Control	Standardized mean difference (95%-CI)[d]	very low / low / acceptable / high[e]
Desired effects	**Crucial outcome measures**									
	Quality of life									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Physical functioning									
	n = 1	high	unknown	no	yes, *n* = 30	no	30		no significant difference compared to control	vey low (6)
	Fatigue									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Pain									
	n = 1	high	unknown	no	yes, *n* = 30	no	30		no significant difference compared to control	vey low (6)
	Important outcome measures									
	Aerobic capacity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Muscle strength									
	n = 1	high	unknown	no	yes, *n* = 30	n.a.	30		no significant difference on hand grip strength compared to control	vey low (6)
	Range of motion									
	n = 1	high	unknown	n.a.	yes, *n* = 30	n.a.	30		no significant difference compared to control	vey low (6)
	Work productivity									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Undesirable effects[f]	**Disease activity**									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Radiological damage									
	n = 0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

n/a: not applicable. **a** Limitations in study design and execution were low in the case of random assignment + allocation concealed + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading took place with a high score. **b** Down-grading took place with I2 > 40%. **c** Down-grading took place in the event of a dichotomous outcome measure with n < 300 and in the case of a continuous outcome measure with *n* < 400. **d** A positive standardised mean difference (SMD) reflects a benefit for the intervention group compared to the control group. If one study measured the respective outcome measure, the results from this study are described. An SMD of < 0.3 is considered as a slight effect of the intervention; 0.3-0.5 as a moderate effect and > 0.5 as a large effect. **e** 1 = down-grading for inconsistency; 2 = down-grading for inaccuracy; 3 = down-grading for inconsistency and inaccuracy; 4 = down-grading for limitations in the study design and method and inconsistency; 5 = down-grading for limitations in study design and method and inaccuracy; 6 = down-grading for limitations in study design and method, inconsistency and inaccuracy. **f** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.

From evidence to recommendation

When formulating the direction and strength of the recommendation for non-exercise therapy interventions, the guideline panel additionally considered the following. See also the assessment form from evidence to recommendation for non-exercise therapy interventions in the appendix to this Note.

- Based on the lack of scientific literature and the low quality of available evidence, the guideline panel determined that the desired and the (possible) undesirable effects are equal. The guideline panel does believe that passive mobilisation can be considered, to support exercise therapy, exclusively as a short-term intervention for increasing joint mobility in patients without active inflammation.
- How much patients value non-exercise therapy interventions and which non-exercise therapy intervention they prefer will differ from patient to patient. The guideline panel estimates that the majority of patients will not have a positive view of non-exercise therapy interventions due to their lack of effectiveness.
- The costs of non-exercise therapy interventions for the patient depend on the current government regulations regarding medical expenses (see Rijksoverheid.nl). In some cases, the physical therapist will incur costs associated with the application of non-exercise therapy interventions because materials and/or equipment must be acquired and because training may be necessary.
- There are no studies available on the cost-effectiveness of non-exercise therapy interventions.
- The guideline panel deems that implementing non-exercise therapy interventions in daily practice is unacceptable and not feasible because the interventions are not viewed as the most indicated treatment option and specific resources may be required for such interventions.

Sources

1. Oldham JA, Stanley JK. Rehabilitation of atrophied muscle in the rheumatoid arthritic hand: a comparison of two methods of electrical stimulation. J Hand Surg Br. 1989;14(3):294-7.
2. Langley GB, Sheppeard H, Johnson M, Wigley RD. The analgesic effects of transcutaneous electrical nerve stimulation and placebo in chronic pain patients. A double-blind non-crossover comparison. Rheumatol Int. 1984;4(3):119-23.
3. Bliddal H, Hellesen C, Ditlevsen P, Asselberghs J, Lyager L. Soft-laser therapy of rheumatoid arthritis. Scand J Rheumatol. 1987;16(4):225-8.
4. Goats GC, Flett E, Hunter JA, Stirling A. Low Intensity Laser and Phototherapy for Rheumatoid Arthritis. Physiotherapy, May 1996, vol82, no 5
5. Hall J, Clarke AK, Elvins DM, Ring EF. Low level laser therapy is ineffective in the management of rheumatoid arthritic finger joints. Br J Rheumatol. 1994;33(2):142-7.
6. Hawkes J, Care G, Dixon JS, Bird HA, Wright VA. Comparison of three different treatments for rheumatoid arthritis of the hands. Physiotherapy Practice 2 1986;2: 155–60,
7. Johannsen F, Hauschild B, Remvig L, Johnsen V, Petersen M, Bieler T. Low energy laser therapy in rheumatoid arthritis. Scand J Rheumatol. 1994;23(3):145-7.
8. Meireles SM, Jones A, Natour J. Low-level laser therapy on hands of patients with rheumatoid arthritis. Clin Rheumatol. 2011;30(1):147-8.
9. Palmgren N, Jensen GF, Kaae K, Windelin M, Colov HC. Low-power laser therapy in rheumatoid arthritis. Lasers Med Sci. 1989 Sep;4(3):193-6.
10. Walker JW, Somlyo AV, Goldman YE, Somlyo AP, Trentham DR. Kinetics of smooth and skeletal muscle activation by laser pulse photolysis of caged inositol 1,4,5-trisphosphate. Nature. 1987;327(6119):249-52.

Note 22. Behavioural interventions for facilitating physical activity

Clinical question

Are (behavioural) interventions for facilitating the degree of physical activity under the supervision of a physical therapist recommended for patients with RA?

Complete clinical question according to PICO

Are (behavioural) interventions for facilitating the degree of physical activity under the supervision of a physical therapist (I) compared to no intervention (C) recommended for patients with RA (P) to improve the degree of physical activity (high to moderate intensity and low intensity), and sedentary behaviour (O)?

Search strategy

On March 3, 2017, the KNGF conducted a search on a summary of the literature (i.e. systematic review) and randomised controlled studies on facilitating physical activity in patients with RA by physical therapists. The search terms for exercise therapy are included in the attachment to this Note. The selection criteria for inclusion are shown in table 22.1.

Table 22.1. Selection criteria for systematic review of behavioural interventions for facilitating physical activity.

Type of study	RCTs
Type of patient	adults diagnosed with rheumatoid arthritis based on the ARA or ACR/EULAR classification criteria
Type of intervention	promotion of physical activity (every form of activity) by a physical therapist
Type of comparison	no intervention or usual care
Type of outcome	degree of physical activity (high to moderate intensity), degree of physical activity (low intensity), sedentary behaviour
Type of timeline	long-term follow-up

Literature found

The literature search yielded 1837 references. One systematic review [1] was identified, which included five randomised controlled studies. This systematic review attained 6 of the 11 points on the AMSTAR checklist. Given the low quality of this review, it was decided to conduct the search again. A total of 24 potential studies were found, of which six randomised controlled studies ultimately met our inclusion criteria.

The flowchart of the systematic review(s) on behavioural interventions for facilitating physical activity is included in the appendix to this Note.[2-7]

Description of studies

The duration of the interventions varied from five weeks to 12 months, with four studies having a relatively short programme (5 to 16 weeks) and two studies having a long programme (one year). Motivational interviewing combined with telephone or SMS reminders was used in two studies. Personalised coaching was used in three studies, with this taking place through an online platform in one study. Educational group sessions were organised in one study.

All studies were aimed at behavioural change, with the following principles being employed:

- Take into account the patient's current phase of behavioural change.
- Establish feasible goals together with the patient.
- Make sure to provide good instructions so that the patient knows and understands what he or she must or can do.
- Ensure sufficient variation during the exercise sessions.
- Integrate individual exercises and physical activities into daily living.
- Ensure that the patient becomes independent of physical therapy support.
- Help the patient avoid lapsing back into his/her old (inactive) exercise behaviour.
- Inform the patient about improvements and teach the patient to monitor his/her improvements him/herself.
- Involve the people in the patient's environment (partner, children, friends, etc.) in supporting changes in the patient's exercise behaviour.
- Encourage the patient to have confidence in his/her own abilities.
- Evaluate together with the patient what has gone well and what has not.
- Help the patient remain focused on his/her own goals and not be distracted by others.
- Teach the patient to deal with negative emotions and stress that could impair achieving the set goals.
- Teach the patient that integrating individual exercises and/or physical activities into daily life is a good way to sustain behavioural change.

Effectiveness and quality of evidence

The assessment of the study design and execution of the selected articles is included in the appendix to this Note.

Below follows a description of the effectiveness of behavioural interventions for facilitating physical activity as well as the quality of evidence for each outcome measure.

Desired effects

Crucial outcome measures

a) 'Degree of moderate-intensity to high-intensity physical activity' outcome measure (4 studies):
   - There is an increased likelihood that behavioural interventions for facilitating physical activity will result in a higher degree of moderate-intensity to high-intensity physical activity compared to no intervention (odds ratio = 1.90; 95%-BI = 1.19-3.05).
   - The quality of evidence for the 'degree of moderate-intensity to high-intensity physical activity' outcome measure is high; no down-grading took place.

b) 'Degree of low-intensity physical activity' outcome measure (3 studies):
   - There is a large effect (SMD = 0.57; 95%-CI = 0.23-0.91) of behavioural interventions on the degree of low-intensity physical activity.
   - The quality of evidence for the 'degree of low-intensity physical activity' outcome measure was lowered by one level to 'acceptable quality of evidence', given the small number of patients (inaccuracy).

c) 'Sedentary behaviour' outcome measure (1 study):
   - The effect of behavioural interventions on sedentary behaviour is unknown (SMD unavailable).
   - The quality of evidence for the 'sedentary behaviour' outcome measure was lowered by two levels to 'low quality of evidence', given the contradictory results (inconsistency) and the small number of patients (inaccuracy).

The GRADE profile of behavioural interventions for facilitating physical activity is shown in table 22.2.

Table 22.2 The GRADE profile of behavioural interventions for facilitating physical activity.

Number of studies	GRADE+					Number of patients		Estimated effect	Quality of evidence
	Limitations in study design and execution[a]	Inconsis-tency[b]	Indirectness	Inaccuracy[c]	Other	Exercise therapy	Control	Standardized mean difference (95%-CI)[d]	very low / low / acceptable / high[e]
Degree of physical activity (moderate intensity to highintensity)									
n = 4	low	no, I^2 = 0%	no	no, *n* = 566	no	265	301	Odds ratio 1.90 (1.19 to 3.05) (n = 3). The Knittle study also found a significant positive effect.	high
Degree of physical activity (low intensity)									
n = 3	low	no, I^2 = 11%	no	yes, *n* = 164	no	83	81	0,57 (0,23 tot 0,91	acceptable (2)
Degree of sedentary behaviour									
n = 1	low	unknown	no	yes, *n* = 20	no	10	10	no significant effect was found for the number of sedentary hours (Thomsen et al., 2016)	low (3)

n/a: not applicable. **a** Limitations in study design and execution were low in the case of random assignment + allocation concealed + intention-to-treat; high in the case of < 3 items assessed positively and moderate in the case of other options. Down-grading took place with a high score. **b** Down-grading took place with I2 > 40%. **c** Down-grading took place in the event of a dichotomous outcome measure with n < 300 and in the case of a continuous outcome measure with *n* < 400. **d** A positive standardised mean difference (SMD) reflects a benefit for the intervention group compared to the control group. If one study measured the respective outcome measure, the results from this study are described. An SMD of < 0.3 is considered as a slight effect of the intervention; 0.3-0.5 as a moderate effect and > 0.5 as a large effect. **e** 1 = down-grading for inconsistency; 2 = down-grading for inaccuracy; 3 = down-grading for inconsistency and inaccuracy; 4 = down-grading for limitations in the study design and method and inconsistency; 5 = down-grading for limitations in study design and method and inaccuracy; 6 = down-grading for limitations in study design and method, inconsistency and inaccuracy. **f** Increased pain, increased disease activity and increased radiological damage in the intervention group compared to the control group are seen as undesirable effects.

From evidence to recommendation

When formulating the direction and strength of the recommendation for behavioural interventions for facilitating physical activity, the guideline panel additionally considered the following. See also the assessment form from evidence to recommendation for behavioural interventions for facilitating physical activity in the appendix to this Note.

The desired effects (improvement of the degree of physical activity and sedentary behaviour) of a behavioural intervention for facilitating the degree of physical activity are presents. No undesirable effects were measured.

- How much patients value behavioural interventions for facilitating physical activity and which intervention they prefer will likely differ from patient to patient.
- The guideline panel estimates that the majority of patients will have a positive view of such interventions due to their favourable effects.
- The costs of behavioural interventions for the patient depend on the current government regulations regarding medical expenses (see Rijksoverheid.nl). The costs of behavioural interventions for facilitating physical activity for the physical therapist and the patient are unknown, but the guideline panel estimates that these costs are not substantial.
- A (12-month) intervention for facilitating physical activity appears to be cost-effective from the patient's perspective but not from the social-societal perspective, except if patients have many limitations in their activities.[8]
- The guideline panel deems that implementing the intervention in daily practice is acceptable and feasible because the intervention is viewed as the most indicated treatment option and no specific resources are required.

Sources

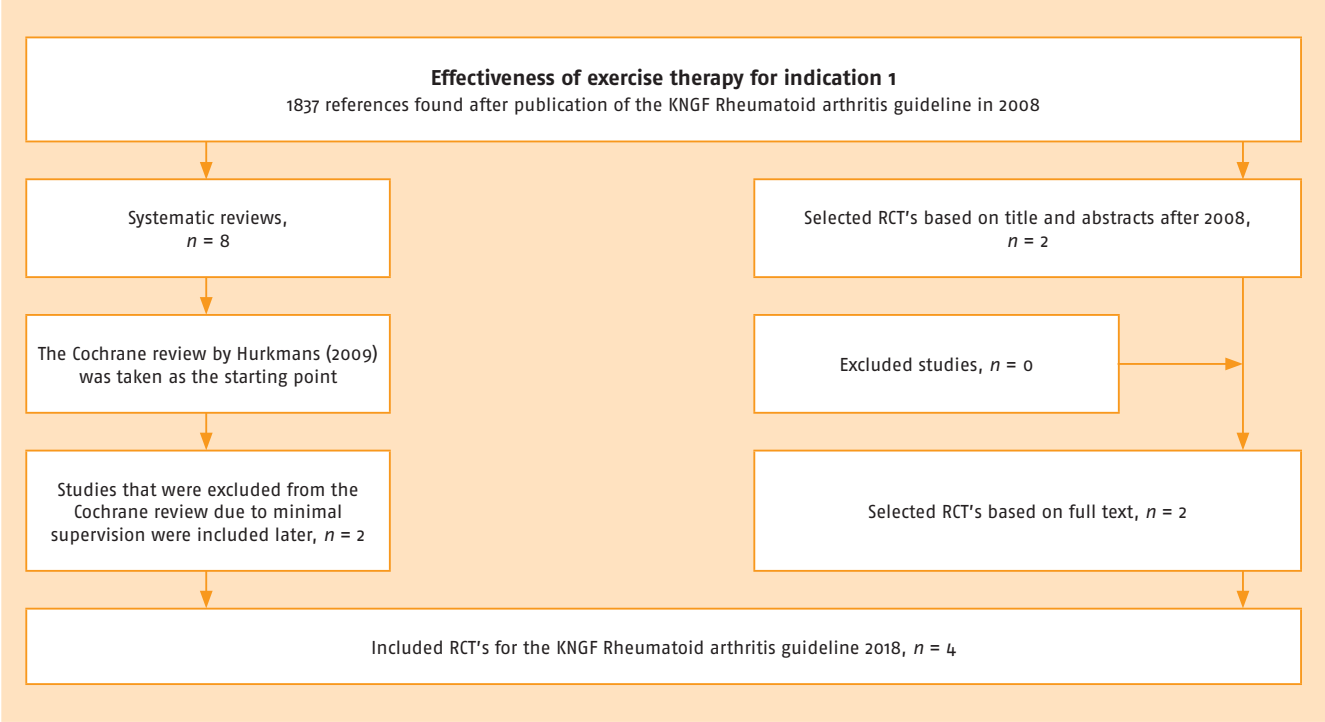
1. Larkin L, Gallagher S, Cramp F, Brand C, Fraser A, Kennedy N. Behaviour change interventions to promote physical activity in rheumatoid arthritis: a systematic review. Rheumatol Int. 2015;35(10):1631-40.
2. Brodin N, Eurenius E, Jensen I, Nisell R, Opava CH. Coaching patients with early rheumatoid arthritis to healthy physical activity: a multicenter, randomized, controlled study. Arthritis Rheum. 2008;59(3):325-31.
3. Feldthusen C, Dean E, Forsblad-d'Elia H, Mannerkorpi K. Effects of person-centered physical therapy on fatigue-related variables in persons with rheumatoid arthritis: a randomized controlled trial. Arch Phys Med Rehabil. 2016 Jan;97(1):26-36.
4. Knittle K, de Gucht V, Hurkmans E, Peeters A, Ronday K, Maes S, et al. Targeting motivation and self-regulation to increase physical activity among patients with rheumatoid arthritis: a randomised controlled trial. Clin Rheumatol. 2015;34(2):231-8.
5. Mayoux-Benhamou A, Giraudet-Le Quintrec JS, Ravaud P, Champion K, Dernis E, Zerkak D, Roy C, Kahan A, Revel M, Dougados M. Influence of patient education on exercise compliance in rheumatoid arthritis: a prospective 12-month randomized controlled trial. J Rheumatol. 2008 Feb;35(2):216-23.
6. Thomsen T, Aadahl M, Beyer N, Hetland ML, Loppenthin K, Midtgaard J, et al. Motivational counselling and SMS-reminders for reduction of daily sitting time in patients with rheumatoid arthritis: a descriptive randomised controlled feasibility study. BMC Musculoskelet Disord. 2016;17(1):434.
7. van den Berg MH, Ronday HK, Peeters AJ, le Cessie S, van der Giesen FJ, Breedveld FC, et al. Using internet technology to deliver a home-based physical activity intervention for patients with rheumatoid arthritis: a randomized controlled trial. Arthritis Rheum. 2006 Dec 15;55(6):935-45.
8. Brodin N, Lohela-Karlsson M, Swardh E, Opava CH. Cost-effectiveness of a one-year coaching program for healthy physical activity in early rheumatoid arthritis. Disabil Rehabil. 2015;37(9):757-62.

Appendices

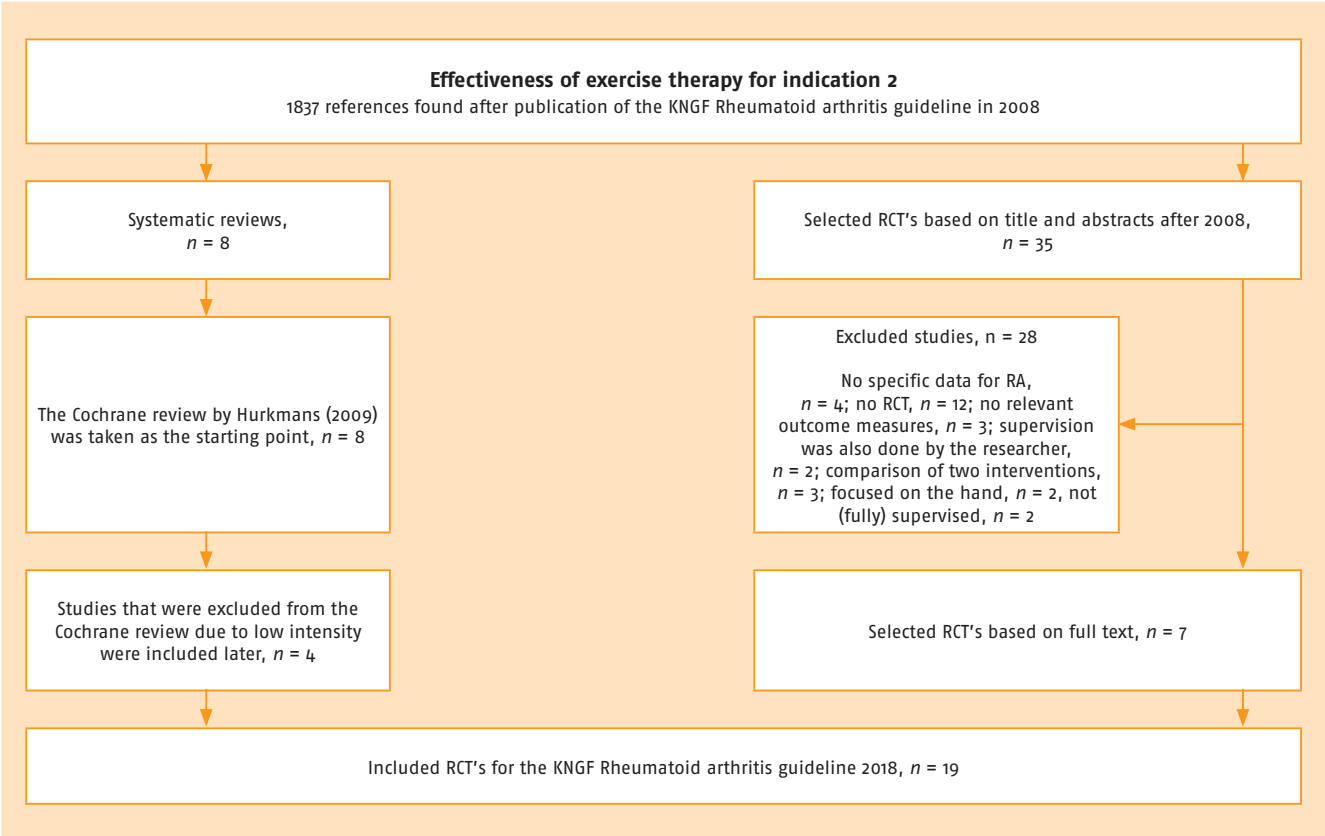
Appendix to Note 10

Exercise therapy search terms (general for the three indications) (see Note 10)	
Search date	3 March 2017
Databases consulted	PubMed, EMBASE, Web of Science, Cochrane Library, CENTRAL, EmCare, CINAHL.
General search terms	(exercis* [tw] OR 'stretching'[tw] OR 'Exercise Therapy'[Mesh] OR 'exercise therapy'[tw] OR exercise therap* [tw] OR 'Muscle Stretching Exercises'[tw] OR 'Muscle Stretching Exercise'[tw] OR 'Static Stretching'[tw] OR 'Passive Stretching'[tw] OR 'Static-Passive Stretching'[tw] OR 'Static Passive Stretching'[tw] OR 'Isometric Stretching'[tw] OR 'Active Stretching'[tw] OR 'Static-Active Stretching'[tw] OR 'Static Active Stretching'[tw] OR 'Ballistic Stretching'[tw] OR 'Dynamic Stretching'[tw] OR 'PNF Stretching'[tw] OR 'Plyometric Exercise'[tw] OR 'Plyometric Exercises'[tw] OR Plyometric Drill* [tw] OR 'Plyometric Drills'[tw] OR 'Plyometric Training'[tw] OR 'Plyometric Trainings'[tw] OR 'Stretch-Shortening Exercise'[tw] OR 'Stretch Shortening Exercise'[tw] OR 'Stretch-Shortening Exercises'[tw] OR 'Stretch-Shortening'[tw] OR 'Stretch Shortening'[tw] OR 'Stretch-Shortening Drills'[tw] OR 'Stretch-Shortening Cycle Exercise'[tw] OR 'Stretch Shortening Cycle Exercise'[tw] OR 'Stretch-Shortening Cycle Exercises'[tw] OR 'Resistance Training'[tw] OR 'Strength Training'[tw] OR 'Weight-Bearing'[tw] OR 'Weight Bearing'[tw] OR 'Exercise'[Mesh] OR 'Exercise'[tw] OR 'Exercises'[tw] OR 'Physical Exercise'[tw] OR 'Physical Exercises'[tw] OR 'Isometric Exercises'[tw] OR 'Isometric Exercise'[tw] OR 'Aerobic Exercises'[tw] OR 'Aerobic Exercise'[tw] OR 'Circuit-Based Exercise'[tw] OR 'Cool-Down Exercise'[tw] OR 'Cool-Down Exercises'[tw] OR 'Physical Conditioning'[tw] OR 'Running'[tw] OR 'Jogging'[tw] OR 'Swimming'[tw] OR 'Walking'[tw] OR 'Warm-Up Exercise'[tw] OR 'Warm-Up Exercises'[tw] OR 'Physical Exertion'[Mesh] OR 'Physical Exertion'[tw] OR 'Physical Effort'[tw] OR 'Physical Efforts'[tw] OR 'Physical Fitness'[Mesh] OR 'Physical Fitness'[tw] OR 'Physical Endurance'[mesh] OR 'Physical Endurance'[tw] OR 'Anaerobic Threshold'[tw] OR 'Exercise Tolerance'[tw] OR 'Exercise Movement Techniques'[Mesh] OR 'Exercise Movement'[tw] OR 'Sports'[Mesh] OR 'Sport'[tw] OR 'Sports'[tw] OR 'Walking'[tw] OR 'Motor Activity'[Mesh] OR 'Physical Activity'[tw] OR exertion* [tw] OR treadmill* [tw] OR swim* [tw] OR bicycl* [tw] OR cycle* [tw] OR cycling[tw] OR walk* [tw] OR muscle strength* [tw])

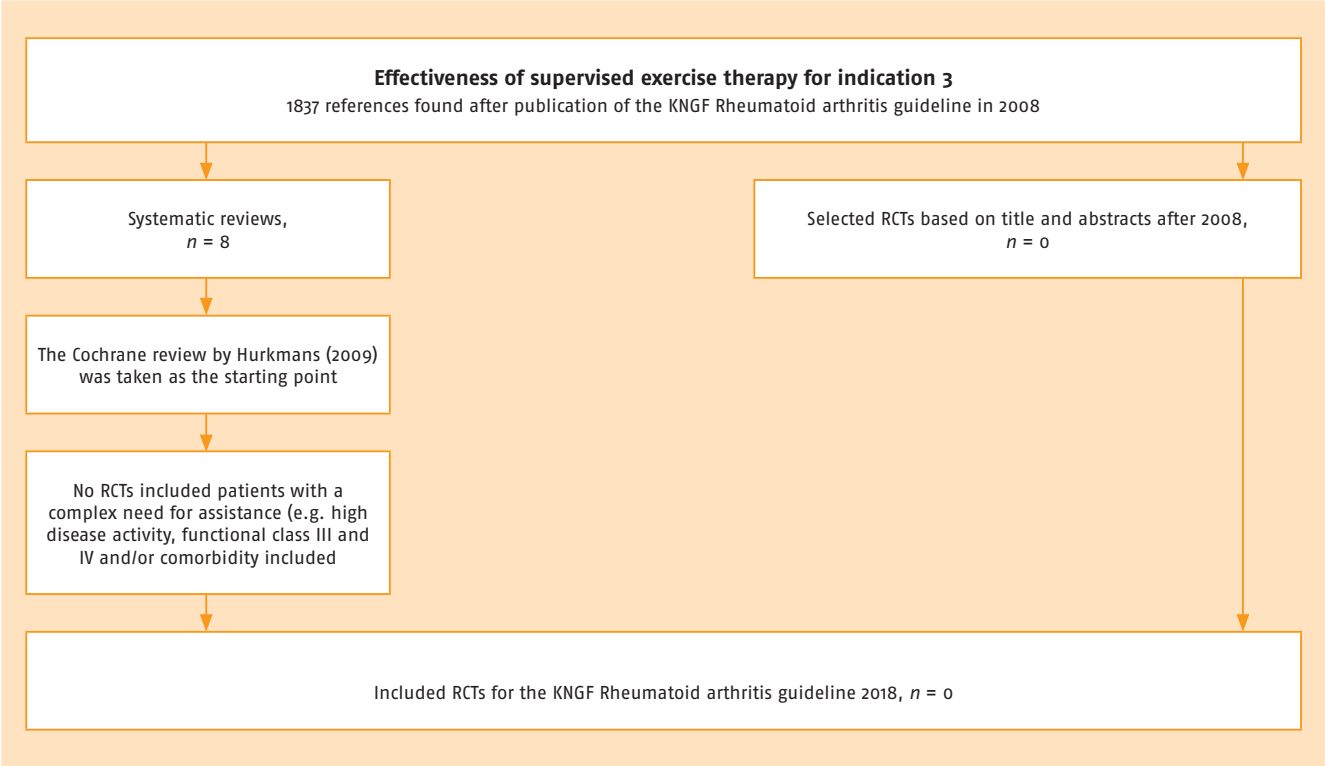
Flowchart of the systematic review for indication 1. Information, advice and instructions for exercise therapy to be done primarily independently (Note 10)



Flowchart of the systematic review for indication 2. Exercise therapy with short-term supervision (Note 10)



Flowchart of the systematic review for indication 3; exercise therapy with intensive supervision (Note 10).



Appendix to Note 11

Assessment of the study design and execution per study for exercise therapy for indication 1 (see Note 11)

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Durcan et al., 2014	+	?	–	?	–	?	+
Häkkinen et al., 2001	+	?	–	?	+	?	+
Stenström et al., 1997	+	?	–	?	–	?	?
Manning et al., 2014	+	+	–	+	+	?	+

+ = yes; – = no; ? = unclear.

Assessment form from evidence to recommendation for exercise therapy for indication 1 (see Note 11)

	Assessment of exercise therapy for indication 1								
Desired effects	slight		moderate		large		varies	unclear	not measured
Undesirable effects	large		moderate		slight		varies	unclear	not measured
Quality of evidence for desired effects	very low	low		acceptable	high		varies	unclear	not measured
Balance between desired and undesirable effects	the undesirable effects definitely outweigh the desired effects	the undesirable effects probably outweigh the desired effects	the desired and undesirable effects are equal	the desired effects probably outweigh	the desired effects definitely outweigh the undesirable effects		varies	unclear	no undesirable effects measured
Value of desired effects	very low	low		acceptable	large		unclear		
Variation in value of desired effects	lots of variation	moderate variation		little variation	no variation		unclear		
Required resources (costs)	high costs	moderate costs	virtually no costs or savings	moderate savings	high savings		varies	unclear	
Variation in required resources (costs)	high	acceptable		low	very low		unclear		
Cost-effectiveness	not cost-effective	probably not cost-effective	intervention and standard care are equal	probably cost-effective	cost-effective		varies	no studies available	
Acceptability	not acceptable	probably not acceptable		probably acceptable	acceptable		varies	unclear	
Feasibility	not realistic	probably not realistic		probably realistic	realistic		varies	unclear	

Appendix to Note 12

Assessment of the study design and execution per study for exercise therapy for indication 2 (see Note 12)

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Baillet et al., 2009	+	+	–	+	+	?	?
Baslund et al., 1993	+	?	–	?	–	?	?
Bearne et al., 2002	+	?	–	?	+	?	+
Bilberg et al., 2005	+	?	–	+	+	?	+
Breedland et al., 2011	+	+	–	+	–	+	+
Da Silva et al., 2013	+	+	–	+	+	+	?
de Jong et al., 2003	+	+	–	+	+	?	+
Flint-Wagner et al., 2009	+	?	–	–	–	?	+
Häkkinen et al., 1994	+	?	–	?	?	?	+
Hansen et al., 1993	+	?	–	+	+	?	?
Harkcom et al., 1985	+	?	–	?	–	?	?
Lemmey et al., 2009	+	?	–	?	+	?	?
Lyngberg et al., 1994	+	?	–	+	–	?	?
McMeeken et al., 1999	+	?	–	+	+	?	+
Minor et al., 1989	+	?	–	?	+	?	?
Sanford-Smith et al., 1998	+	?	–	+	+	?	?
Siquira et al., 2016	+	+	–	+	+	?	+
Strasser et al., 2011	+	?	–	?	–	?	+
Van den Ende et al., 1996	+	?	–	?	+	?	?

+ = yes; – = no; ? = unclear.

Assessment form from evidence to recommendation for exercise therapy for indication 2 (see Note 12)

	Assessment of exercise therapy for indication 2								
Desired effects	slight		moderate		large		varies	unclear	not measured
Undesirable effects	large		moderate		slight		varies	unclear	not measured
Quality of evidence for desired effects	very low	low		acceptable	high		varies	unclear	not measured
Balance between desired and undesirable effects	the undesirable effects definitely outweigh the desired effects	the undesirable effects probably outweigh the desired effects	the desired and undesirable effects are equal	the desired effects probably outweigh	the desired effects definitely outweigh the undesirable effects		varies	unclear	no undesirable effects measured
Value of desired effects	very low	low		acceptable	large		unclear		
Variation in value of desired effects	lots of variation	moderate variation		little variation	no variation		unclear		
Required resources (costs)	high costs	moderate costs	virtually no costs or savings	moderate savings	high savings		varies	unclear	
Variation in required resources (costs)	high	moderate		low	very low		unclear		
Cost-effectiveness	not cost-effective	probably not cost-effective	intervention and standard care are equal	probably cost-effective	cost-effective		varies	no studies available	
Acceptability	not acceptable	the majority not acceptable		the majority acceptable	acceptable		varies	unclear	
Feasibility	not realistic	the majority not realistic		the majority realistic	realistic		varies	unclear	

Appendix to Note 13

Assessment form from evidence to recommendation for exercise therapy for indication 3 (see Note 13)

	Assessment of exercise therapy for indication 3								
Desired effects	slight		moderate		large		varies	unclear	not measured
Undesirable effects	large		moderate		slight		varies	unclear	not measured
Balance between desired and undesirable effects	the undesirable effects definitely outweigh the desired effects	the undesirable effects probably outweigh the desired effects	the desired and undesirable effects are equal	the desired effects probably outweigh	the desired effects definitely outweigh the undesirable effects		varies	unclear	no undesirable effects measured
Value for patients of outcome measures	very low	low	acceptable	large			unclear		
Variation in value for patients of outcome measures	lots of variation	moderate variation	little variation	no variation			unclear		
Required resources (costs)	high costs	moderate costs	virtually no costs or savings	moderate savings	high savings		varies	unclear	
Variation in required resources (costs)	high	moderate	low	very low			unclear		
Acceptability	not acceptable	probably not acceptable	probably acceptable	acceptable			varies	unclear	
Feasibility	not realistic	probably not realistic	probably realistic	realistic			varies	unclear	

Appendix to Note 14

ZoeSearch terms (general for all FITT principles) (see Note 14)	
Search date	3 March 2017
Databases consulted	PubMed, EMBASE, Web of Science, Cochrane Library, CENTRAL, EmCare, CINAHL.
General search terms	(exercis* [tw] OR 'stretching'[tw] OR 'Exercise Therapy'[Mesh] OR 'exercise therapy'[tw] OR exercise therap* [tw] OR 'Muscle Stretching Exercises'[tw] OR 'Muscle Stretching Exercise'[tw] OR 'Static Stretching'[tw] OR 'Passive Stretching'[tw] OR 'Static-Passive Stretching'[tw] OR 'Static Passive Stretching'[tw] OR 'Isometric Stretching'[tw] OR 'Active Stretching'[tw] OR 'Static-Active Stretching'[tw] OR 'Static Active Stretching'[tw] OR 'Ballistic Stretching'[tw] OR 'Dynamic Stretching'[tw] OR 'PNF Stretching'[tw] OR 'Plyometric Exercise'[tw] OR 'Plyometric Exercises'[tw] OR Plyometric Drill* [tw] OR 'Plyometric Drills'[tw] OR 'Plyometric Training'[tw] OR 'Plyometric Trainings'[tw] OR 'Stretch-Shortening Exercise'[tw] OR 'Stretch Shortening Exercise'[tw] OR 'Stretch-Shortening Exercises'[tw] OR 'Stretch-Shortening'[tw] OR 'Stretch Shortening'[tw] OR 'Stretch-Shortening Drills'[tw] OR 'Stretch-Shortening Cycle Exercise'[tw] OR 'Stretch Shortening Cycle Exercise'[tw] OR 'Stretch-Shortening Cycle Exercises'[tw] OR 'Resistance Training'[tw] OR 'Strength Training'[tw] OR 'Weight-Bearing'[tw] OR 'Weight Bearing'[tw] OR 'Exercise'[Mesh] OR 'Exercise'[tw] OR 'Exercises'[tw] OR 'Physical Exercise'[tw] OR 'Physical Exercises'[tw] OR 'Isometric Exercises'[tw] OR 'Isometric Exercise'[tw] OR 'Aerobic Exercises'[tw] OR 'Aerobic Exercise'[tw] OR 'Circuit-Based Exercise'[tw] OR 'Cool-Down Exercise'[tw] OR 'Cool-Down Exercises'[tw] OR 'Physical Conditioning'[tw] OR 'Running'[tw] OR 'Jogging'[tw] OR 'Swimming'[tw] OR 'Walking'[tw] OR 'Warm-Up Exercise'[tw] OR 'Warm-Up Exercises'[tw] OR 'Physical Exertion'[Mesh] OR 'Physical Exertion'[tw] OR 'Physical Effort'[tw] OR 'Physical Efforts'[tw] OR 'Physical Fitness'[Mesh] OR 'Physical Fitness'[tw] OR 'Physical Endurance'[mesh] OR 'Physical Endurance'[tw] OR 'Anaerobic Threshold'[tw] OR 'Exercise Tolerance'[tw] OR 'Exercise Movement Techniques'[Mesh] OR 'Exercise Movement'[tw] OR 'Sports'[Mesh] OR 'Sport'[tw] OR 'Sports'[tw] OR 'Walking'[tw] OR 'Motor Activity'[Mesh] OR 'Physical Activity'[tw] OR exertion* [tw] OR treadmill* [tw] OR swim* [tw] OR bicycl* [tw] OR cycle* [tw] OR cycling[tw] OR walk* [tw] OR muscle strength* [tw])

Appendix to Note 15

Assessment of the study design and execution per study for the frequency of exercise therapy (see Note 15)

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Baillet et al., 2009	+	+	–	+	+	?	?
Baslund et al., 1993	+	?	–	?	–	?	?
Bearne et al., 2002	+	?	–	?	+	?	+
Bilberg et al., 2005	+	?	–	+	+	?	+
Breedland et al., 2011	+	+	–	+	–	+	+
Da Silva et al., 2013	+	+	–	+	+	+	?
De Jong et al., 2003	+	+	–	+	+	?	+
Flint-Wagner et al., 2009	+	?	–	–	–	?	+
Häkkinen et al., 1994	+	?	–	?	?	?	+
Hansen et al., 1993	+	?	–	+	+	?	?
Harkcom et al., 1985	+	?	–	?	–	?	?
Lemmey et al., 2009	+	?	–	?	+	?	?
Lyngberg et al., 1994	+	?	–	+	–	?	?
McMeeken et al., 1999	+	?	–	+	+	?	+
Minor et al., 1989	+	?	–	?	+	?	?
Sanford-Smith et al., 1998	+	?	–	+	+	?	?
Siquira et al., 2016	+	+	–	+	+	?	+
Strasser et al., 2011	+	?	–	?	–	?	+
van den Ende et al., 1996	+	?	–	?	+	?	?

+ = yes; – = no; ? = unclear.

Appendix to Note 16

Assessment of the study design and execution per study for the intensity of exercise therapy (see Note 16)

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Bostrom et al., 1998	+	?	-	+	+	?	+
Ekdahl et al., 1990	+	?	-	+	+	?	+
Van den Ende et al., 1996	+	?	-	?	+	?	?
Van den Ende et al., 2000	+	+	-	+	+	?	+

+ = yes; – = no; ? = unclear.

Appendix to Note 18

Assessment of the study design and execution per study for the duration of exercise therapy (see Note 18)

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Baillet et al., 2009	+	+	–	+	+	?	?
Baslund et al., 1993	+	?	–	?	–	?	?
Bearne et al., 2002	+	?	–	?	+	?	+
Bilberg et al., 2005	+	?	–	+	+	?	+
Breedland et al., 2011	+	+	–	+	–	+	+
Da Silva et al., 2013	+	+	–	+	+	+	?
De Jong et al., 2003	+	+	–	+	+	?	+
Flint-Wagner et al., 2009	+	?	–	–	–	?	+
Hakkinen et al., 1994	+	?	–	?	?	?	+
Hansen et al., 1993	+	?	–	+	+	?	?
Harkcom et al., 1985	+	?	–	?	–	?	?
Lemmey et al., 2009	+	?	–	?	+	?	?
Lyngberg et al., 1994	+	?	–	+	–	?	?
McMeeken et al., 1999	+	?	–	+	+	?	+
Minor et al., 1989	+	?	–	?	+	?	?
Sanford-Smith et al., 1998	+	?	–	+	+	?	?
Siquira et al., 2016	+	+	–	+	+	?	+
Strasser et al., 2011	+	?	–	?	–	?	+
Van den Ende et al., 1996	+	?	–	?	+	?	?

+ = yes; – = no; ? = unclear.

Appendix to Note 19

Assessment of the study design and execution per study for hand exercises (see Note 19)

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Dogu et al., 2013	+	?	–	+	+	?	?
Cima et al., 2013	+	?	–	–	?	?	+
Lamb et al., 2015	+	+	–	+	+	+	+
O'Brien et al., 2006	+	?	–	+	–	?	+

+ = yes; – = no; ? = unclear.

Assessment of the study design and execution per study for exercise therapy on land versus exercise therapy in water (see Note 19)

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Minor et al., 1989	+	?	–	?	+	?	?
Siqueira et al., 2017	+	+	–	+	+	?	+

+ = yes; – = no; ? = unclear.

Appendix to Note 21

Search terms for non-exercise therapy interventions (see Note 21)	
Search date	3 March 2017
Databases consulted	PubMed, EMBASE, Web of Science, Cochrane Library, CENTRAL, EmCare, CINAHL.
Passive mobilisation search terms	('Continuous Passive Motion Therapy'[tw] OR 'Continuous Passive Movement'[tw] OR 'CPM Therapy'[tw] OR 'Passive Stretching'[tw] OR 'PNF Stretching'[tw] OR 'musculoskeletal manipulations'[Mesh:NoExp] OR 'musculoskeletal manipulations'[tw] AND 'Arthritis, Rheumatoid'[Mesh] OR 'rheumatoid arthritis'[tw] OR 'arthritis'[Mesh] OR 'arthritis'[tw] OR 'rheumatic disorder'[tw] OR 'rheumatic disease'[tw]) AND ('Arthritis, Rheumatoid'[Mesh] OR 'rheumatoid arthritis'[tw] OR 'arthritis'[Mesh] OR 'arthritis'[tw] OR 'rheumatic disorder'[tw] OR 'rheumatic disease'[tw])
Massage search terms	('massage'[Mesh] OR 'massage'[tw]) AND ('Arthritis, Rheumatoid'[Mesh] OR 'rheumatoid arthritis'[tw] OR 'arthritis'[Mesh] OR 'arthritis'[tw] OR 'rheumatic disorder'[tw] OR 'rheumatic disease'[tw])
Thermotherapy search terms	('thermotherapy'[tw] OR 'hot packs'[tw] OR 'cold packs'[tw] OR 'cold treatment'[tw] OR 'heat treatment'[tw]) AND ('Arthritis, Rheumatoid'[Mesh] OR 'rheumatoid arthritis'[tw] OR 'arthritis'[Mesh] OR 'arthritis'[tw] OR 'rheumatic disorder'[tw] OR 'rheumatic disease'[tw])
Electric, electromagnetic and mechanical energy	('Electric stimulation therapy'[Mesh:NoExp] OR electric stimulation therapy'[tw] OR 'electrical stimulation therapy'[tw] OR 'therapeutic electric stimulation'[tw] OR 'therapeutic electrical stimulation'[tw] OR 'electrotherapy'[tw] OR 'interferential current electrotherapy'[tw] OR 'electrical stimulation'[tw] OR 'electrical nerve stimulation'[tw] OR 'transcutaneous electric nerve stimulation'[Mesh:NoExp] OR 'transcutaneous electric nerve stimulation'[tw] OR 'therapeutic ultrasound'[tw] OR 'ultrasound'[tw] OR 'ultrasonic therapy'[tw] OR 'electromagnetic therapy'[tw]) OR AND ('low level laser therapy'[tw] OR 'low level laser treatment'[tw] OR 'low intensity laser'[tw] OR 'soft-laser therapy'[tw] OR 'low energy laser therapy'[tw] OR 'low-power laser therapy'[tw])) AND ('Arthritis, Rheumatoid'[Mesh] OR 'rheumatoid arthritis'[tw] OR 'arthritis'[Mesh] OR 'arthritis'[tw] OR 'rheumatic disorder'[tw] OR 'rheumatic disease'[tw])
Medical taping search terms	(medical taping OR taping OR kinesiotaping) AND ('Arthritis, Rheumatoid'[Mesh] OR 'rheumatoid arthritis'[tw] OR 'arthritis'[Mesh] OR 'arthritis'[tw] OR 'rheumatic disorder'[tw] OR 'rheumatic disease'[tw])
Dry needling search terms	dry needling AND ('Arthritis, Rheumatoid'[Mesh] OR 'rheumatoid arthritis'[tw] OR 'arthritis'[Mesh] OR 'arthritis'[tw] OR 'rheumatic disorder'[tw] OR 'rheumatic disease'[tw])

Assessment of the study design and execution per study for non-exercise therapy interventions (see Note 21)

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Electrostimulation							
Oldham et al., 1989	+	?	–	?	+	?	+
TENS							
Langley et al., 1984	+	–	–	+	?	?	+
Electromagnetic energy (low-level laser therapy)							
Bliddal et al., 1987	+	?	+	?	?	?	+
Goats et al., 1996	+	+	+	?	?	?	–
Hall et al., 1994	+	?	+	+	–	?	?
Johanssen et al., 1994	+	+	?	+	?	?	+
Meireles et al., 2010	+	?	+	+	?	+	+
Palmgren et al., 1989	+	?	+	?	–	?	?
Walker et al., 1987	+	?	–	?	–	?	?
Mechanical energy (ultrasound)							
Hawkes et al., 1986	+	–	–	+	–	?	?

+ = yes; – = no; ? = unclear.

Assessment form from evidence to recommendation for non-exercise therapy interventions (see Note 21)

	Effectiveness of non-exercise therapy interventions								
Desired effects	slight		moderate		large		varies	unclear	not measured
Undesirable effects	large		moderate		slight		varies	unclear	not measured
Quality of desired effects	very low	low		acceptable		high	varies	unclear	not measured
Balance between desired and undesirable effects	the undesirable effects definitely outweigh the desired effects	the undesirable effects probably outweigh the desired effects	the desired and undesirable effects are equal	the desired effects probably outweigh	the desired effects definitely outweigh the undesirable effects		varies	unclear	no undesirable effects measured
Value of desired effects	very low	low		acceptable		large	unclear		
Variation in value of desired effects	lots of variation		moderate variation		little variation	no variation	unclear		
Required resources (costs)	high costs	moderate costs	virtually no costs or savings	moderate savings	high savings		varies	unclear	
Variation in required resources (costs)	high		moderate		low	very low	unclear		
Acceptability	not acceptable		probably not acceptable		probably acceptable	acceptable	varies	no idea	
Feasibility	not realistic		probably not realistic		probably realistic	realistic	varies	no idea	

Appendix to Note 22

Search terms for behavioural interventions for facilitating physical activity (see Note 22)

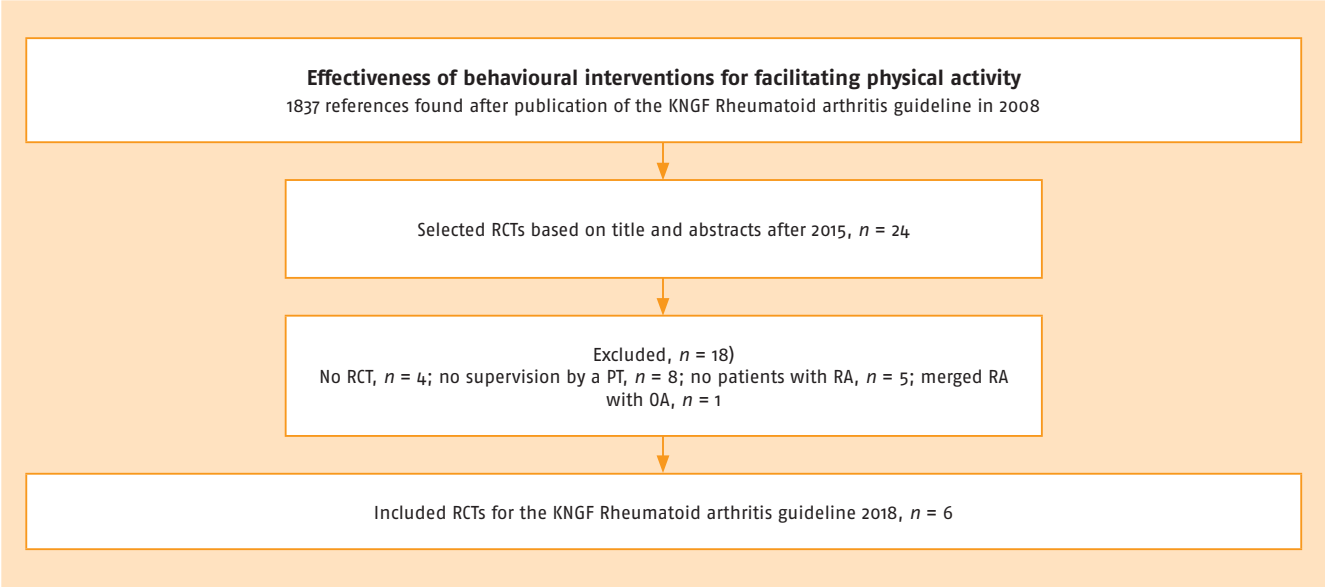
Search date	3 March 2017
Databases consulted	PubMed, EMBASE, Web of Science, Cochrane Library, CENTRAL, EmCare, CINAHL.
General search terms	(exercis* [tw] OR 'stretching'[tw] OR 'Exercise Therapy'[Mesh] OR 'exercise therapy'[tw] OR exercise therap* [tw] OR 'Muscle Stretching Exercises'[tw] OR 'Muscle Stretching Exercise'[tw] OR 'Static Stretching'[tw] OR 'Passive Stretching'[tw] OR 'Static-Passive Stretching'[tw] OR 'Static Passive Stretching'[tw] OR 'Isometric Stretching'[tw] OR 'Active Stretching'[tw] OR 'Static-Active Stretching'[tw] OR 'Static Active Stretching'[tw] OR 'Ballistic Stretching'[tw] OR 'Dynamic Stretching'[tw] OR 'PNF Stretching'[tw] OR 'Plyometric Exercise'[tw] OR 'Plyometric Exercises'[tw] OR Plyometric Drill* [tw] OR 'Plyometric Drills'[tw] OR 'Plyometric Training'[tw] OR 'Plyometric Trainings'[tw] OR 'Stretch-Shortening Exercise'[tw] OR 'Stretch Shortening Exercise'[tw] OR 'Stretch-Shortening Exercises'[tw] OR 'Stretch-Shortening'[tw] OR 'Stretch Shortening'[tw] OR 'Stretch-Shortening Drills'[tw] OR 'Stretch-Shortening Cycle Exercise'[tw] OR 'Stretch Shortening Cycle Exercise'[tw] OR 'Stretch-Shortening Cycle Exercises'[tw] OR 'Resistance Training'[tw] OR 'Strength Training'[tw] OR 'Weight-Bearing'[tw] OR 'Weight Bearing'[tw] OR 'Exercise'[Mesh] OR 'Exercise'[tw] OR 'Exercises'[tw] OR 'Physical Exercise'[tw] OR 'Physical Exercises'[tw] OR 'Isometric Exercises'[tw] OR 'Isometric Exercise'[tw] OR 'Aerobic Exercises'[tw] OR 'Aerobic Exercise'[tw] OR 'Circuit-Based Exercise'[tw] OR 'Cool-Down Exercise'[tw] OR 'Cool-Down Exercises'[tw] OR 'Physical Conditioning'[tw] OR 'Running'[tw] OR 'Jogging'[tw] OR 'Swimming'[tw] OR 'Walking'[tw] OR 'Warm-Up Exercise'[tw] OR 'Warm-Up Exercises'[tw] OR 'Physical Exertion'[Mesh] OR 'Physical Exertion'[tw] OR 'Physical Effort'[tw] OR 'Physical Efforts'[tw] OR 'Physical Fitness'[Mesh] OR 'Physical Fitness'[tw] OR 'Physical Endurance'[mesh] OR 'Physical Endurance'[tw] OR 'Anaerobic Threshold'[tw] OR 'Exercise Tolerance'[tw] OR 'Exercise Movement Techniques'[Mesh] OR 'Exercise Movement'[tw] OR 'Sports'[Mesh] OR 'Sport'[tw] OR 'Sports'[tw] OR 'Walking'[tw] OR 'Motor Activity'[Mesh] OR 'Physical Activity'[tw] OR exertion* [tw] OR treadmill* [tw] OR swim* [tw] OR bicycl* [tw] OR cycle* [tw] OR cycling[tw] OR walk* [tw] OR muscle strength* [tw])

Assessment of the study design and execution per study for behavioural interventions for facilitating physical activity (see Note 22)

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Brodin	+	?	–	+	–	+	+
Feldhusen	+	+	–	+	+	+	+
Knittle	+	+	–	?	+	+	+
Mayoux	+	+	–	+	+	?	+
Thomsen	+	+	–	+	+	+	+
Van den Berg	+	+	–	+	+	?	+

+ = yes; – = no; ? = unclear.

Flowchart of the systematic review of behavioural interventions for facilitating physical activity (see Note 22)



Assessment form from evidence to recommendation for behavioural interventions for facilitating physical activity (see Note 22)

	Assessment of behavioural interventions for facilitating physical activity								
Desired effects	slight		moderate		large		varies	unclear	not measured
Undesirable effects	large		moderate		slight		varies	unclear	not measured
Quality of desired effects	very low	low		acceptable		high	varies	unclear	not measured
Balance between desired and undesirable effects	the undesirable effects definitely outweigh the desired effects	the undesirable effects probably outweigh the desired effects	the desired and undesirable effects are equal	the desired effects probably outweigh	the desired effects definitely outweigh the undesirable effects		varies	unclear	no undesirable effects measured
Value of desired effects	very low	low		acceptable		large	unclear		
Variation in value of desired effects	lots of variation		moderate variation		little variation	no variation	unclear		
Required resources (costs)	high costs	moderate costs	virtually no costs or savings	moderate savings	high savings		varies	unclear	
Variation in required resources (costs)	high		moderate		low	very low	unclear		
Cost-effectiveness	not cost-effective	probably not cost-effective	intervention and standard care are equal	probably cost-effective	cost-effective		varies	no studies available	
Acceptability	not acceptable		probably not acceptable		probably acceptable	acceptable	varies	unclear	
Feasibility	not realistic		probably not realistic		probably realistic	realistic	varies	unclear	

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