Justification

KNGF Guideline on Low Back Pain and Lumbosacral Radicular Syndrome

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Koninklijk Nederlands Genootschap voor Fysiotherapie

Royal Dutch Society for Physical Therapy

Vereniging van Oefentherapeuten

Amersfoort, October 2021

All sections of the guideline, including the summary, are available at **kngf.nl/kennisplatform**

Koninklijk Nederlands Genootschap voor Fysiotherapie

Royal Dutch Society for Physical Therapy

VvOCM

Vereniging van Oefentherapeuten

The KNGF Guideline on Low Back Pain and Lumbosacral Radicular Syndrome is a publication of the Royal Dutch Society for Physical Therapy (Koninklijk Nederlands Genootschap voor Fysiotherapie – KNGF) and the Association of Cesar and Mensendieck Exercise Therapists (Vereniging van Oefentherapeuten Cesar en Mensendieck – VvOCM).

Please site this guideline as follows: KNGF Guideline on Low Back Pain and Lumbosacral Radicular Syndrome. Amersfoort/Utrecht: KNGF/VvoCM; 2021.

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Note A.1 Introduction

Application of the KNGF guideline methodology

This guideline was developed in accordance with the 2019 KNGF Guideline Methodology (KNGF 2019). This methodology is based on the AGREE II instrument and the AQUA guideline (Brouwers 2010; Healthcare Institute of the Netherlands 2021). GRADE is used within the KNGF guideline methodology for assessing the evidentiary value and for the evidence-to-decision process (Alonso-Coello 2016a,b; Andrews 2013; Atkins 2004). The experts involved (Dr A. Apeldoorn, Prof. R. Ostelo and the KNGF) evaluate on a yearly basis whether substantive and/or policy developments necessitate a (modular) revision of the guideline.

Preparation phase

As a first step, a guideline panel and a review panel were set up containing representation from the relevant stakeholders. The core group members and all guideline panel and review panel members signed a declaration of interests at the start and at the completion of the project (see appendix A.1-1 and A.1-2 for an overview of the interests).
For the purposes of identifying the barriers, two focus groups were organised in which 18 physical therapists and exercise therapists took part, and five patients completed the questionnaires with this goal. These barriers were presented to the members of the guideline panel and review panel during their separate meetings, during which the barriers of the members themselves were also identified. All of these barriers were then prioritised and converted into clinical questions by the core group in collaboration with the guideline panel.

Development phase

As a basis for the guideline, the guidelines for low back pain and sciatica that are of high methodological quality were used as much as possible, and the British (multidisciplinary) guideline 'Low back pain and sciatica in over 16s: assessment and management' was selected, a guideline that is published by the National Institute for Health and Care Excellence (NICE) and focuses on low back pain with or without sciatica (De Campos 2017).
In addition to this, a systematic search was carried out for systematic reviews on patients with low back pain and for evidence-based guidelines for patients with low back pain that were published after the publication of this NICE guideline. The search was carried out on 14 April 2020 by an information specialist (J.W. Schoones, Leiden University Medical Centre) in PubMed, MEDLINE, Embase, Emcare, Web of Science and the Cochrane Library (see appendix A.1-3 for the search rationale). This search produced 2,439 unique hits. The results were supplemented by the findings from the Dutch-language evidence-based guidelines on treating patients with low back pain that were not included in the above databases (Luites 2021; Dutch Orthopaedic Association [Nederlandse Orthopaedische Vereniging] 2017; Dutch Neurosurgical Society [Nederlandse Vereniging voor Neurochirurgie] 2018; Netherlands Society for Neurology [Nederlandse Vereniging voor Neurologie] 2020; NHG Guideline Panel for the Standard on Non-specific Low Back Pain [NHG-Werkgroep Standaard Aspecifieke lagerugpijn] 2017; Perez 2017; Schaafstra 2015; Van Tulder 2010). For each clinical question, an assessment was done to see whether there were systematic reviews among these unique hits with which the clinical question could be answered, whether the studies met the inclusion criteria and whether the studies were sufficiently current and whether the studies were of sufficient methodological quality.

If such systematic reviews were lacking, and if the clinical question was eligible for this, the core group carried out a systematic review itself. PICOs were compiled to this end, and a new search was carried out by the same information specialist in the above-mentioned databases. By means of pre-established inclusion and exclusion criteria, the encountered studies were selected based on – successively – title and abstract and then on the complete text. The subject-matter expert scientist (AA) involved in the guideline or the KNGF guideline advisor (NS) then extracted the data, analysed the data and assessed the evidentiary value according to the GRADE method (Higgins 2021). With regard to the clinical question about TENS and interference, support was offered by Jesús Diaz Merino (Hanze University of Applied Sciences Groningen) and for the clinical question about mobilisations and manipulations by Dr Sidney Rubinstein (Department of Health Sciences, Faculty of Science, VU Amsterdam).
As a last step, conclusions were drawn based on the literature aligned with the scope of the effect and the evidentiary value. For each outcome measure, the evidentiary value was assessed for the following using GRADE:

- limitations in the study design and implementation: for example, due to randomisation errors or a lack of follow-up;
- inconsistency: when the results of the various studies vary in magnitude and/or direction of the effect and this heterogeneity cannot be explained; the confidence intervals do not overlap or barely overlap;
- indirectness: if the found evidence does not (entirely) align with one or more PICO elements, for example if intermediate or surrogate outcome measures (O) are used or if no direct comparison of the experimental and standard intervention is available (I-C);
- inaccuracy of the estimated effect due to a small study group and/or few events, resulting in wide confidence intervals;
- publication bias: for example, if it is plausible that studies with negative results were not submitted for publication.

The GRADE system has four levels of evidentiary value: 'high', 'moderate', 'low' or 'very low'.

Interpretation of the evidentiary value

High	The actual effect is close to the estimation of the effect.
Moderate	The actual effect is likely close to the estimation of the effect, but it is possible for the actual effect to substantially deviate from the estimation of the effect.
Low	The actual effect may differ substantially from the estimation of the effect.
Very low	The actual effect likely differs substantially from the estimation of the effect.

The following format was used to interpret the scope of the effect as an indication and in consultation with the guideline panel:

Interpretation of the scope of the effect

	Small effect	Moderate effect*	Large effect
Standardized mean difference (SMD)	< 0.3	0.3 to 0.5	> 0,5
VAS/NPRS (0–100) MD	< 10	10 to 20	> 20
RMDQ (0–24) MD	< 2	2 to 5	> 5
ODI/QBPDS (0–100) MD	< 10	10 to 20	> 20
Quality of life (SF–12, PCS 0–100)	< 10	10 to 20	> 20
Quality of life (SF–12, MCS 0–100)	< 10	10 to 20	> 20

These values are commensurate with the guideline of the National Institute for Health and Care Excellence (De Campos 2017) and the KNGF Guideline on Rheumatoid Arthritis (KNGF 2018).
MD = mean difference; NPRS = Numeric Pain Rating Scale; ODI = Oswestry Disability Index; QBPDS = Quebec Back Pain Disability Scale; RMDQ = 'Roland Morris Disability Questionnaire; SF–36; 36–items Short Form Health Survey; VAS = Visual Analogue Scale.
* The lower limit of a moderate effect is also considered to be clinically relevant.

After the evidentiary value and magnitude of the effect were determined, sub-groups of guideline panel and review panel members formulated the remaining considerations, which were then discussed in eight meetings with the guideline panel and six meetings with the review panel based on the GRADE evidence-to-decision process (Alonso-Coello 2016a,b) until consensus was achieved. Based on the scientific evidence and the other considerations, the direction and strength of the recommendation were then determined. Finally, based on this, the recommendation should preferably be formulated as follows:

Example of the formulation of the recommendation

Type of recommendation	Formulation
Strongly positive	'Apply…' / 'Implement…' / 'Offer…'
Weak/conditionally positive	'Preferably apply…' (condition)' / 'Take into consideration…' / 'Consider…'
Weak/conditionally negative	'Preferably do not apply…' (condition)' / 'Take into consideration…' / 'Consider…' / 'Be cautious in…'
Strongly negative	'Do not apply…' / 'Do not implement…' / 'Do not offer…'

The complete search strategy, the results of the systematic review and – if applicable – the completed evidence-to-decision form was included in the respective clinical question.
The concept guideline is compiled through all recommendations, including the system of notes (the Explanation) and this Justification.

External review and authorisation phase

The concept guideline was sent to a number of selected physical therapists and exercise therapists (as well as to the Scientific College of Physical Therapy [Wetenschappelijk College Fysiotherapie – WCF]) and involved associations of professional content (APCs) and to other professional groups and other stakeholders who are involved in caring for patients with low back pain.
The collected comments were summarised in a comments table, which was presented to the guideline panel. The guideline panel determined which changes and/or additions were required or desired to be made to the concept guideline. The review panel advised on this as well. After being adopted by the guideline panel and the review panel, the guideline was presented to all involved stakeholders for authorisation.

Dissemination and implementation phase

Implementation of the guideline entails development of the following products:

- patient information;
- lecture;
- workshop;
- e-learning;
- knowledge gaps;
- articles in magazines (both within and outside the fields of physical therapy and exercise therapy both nationally and internationally);
- lectures at congresses and symposia.

Implementation activities are aimed in particular at the following five core topics:

1. prognostic factors and treatment profiles;
2. lumbosacral radicular syndrome, diagnostics and treatment;
3. Information and advice and pain education, contents of the information and advice;
4. exercise therapy interventions;
5. behaviour-oriented treatment.

Involvement of stakeholders

Therapists

The primary users of the guideline are physical therapists and exercise therapist C/M. They made an important contribution to the guideline in all phases of its development. For example, therapists indicated barriers in the preparation phase, sat on the guideline panel and review panel in the development phase, provided comments on the concept guideline in the external review phase and provided feedback on the implementation products during the implementation phase.

Patients

In order to guarantee the patient perspective to the greatest extent possible, patients were involved in the guideline development as early as during the preparation phase. Patients indicated barriers by means of a questionnaire. These barriers, along with the barriers flagged by the therapists and the guideline panel and review panel, served as the basis for the clinical questions. A representative of the Dutch Association of Back Patients 'the Spine' (Nederlandse Vereniging

van Rugpatiënten de Wervelkolom) took part in the development process, as part of the guideline panel and during the external review phase. This patient association was also involved in the development of the patient information.

Other stakeholders

A number of other stakeholders sat on the guideline panel or review panel and/or were involved in the guideline during the external review phase and contributed to the creation of the guideline in this way.

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Note A.2.1 Epidemiology, pathophysiology and co-morbidity

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Note A.2.2 Societal impact

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Note A.2.3 Clinical presentation and course

See appendix A.2.3-1 for a literature overview regarding the course of low back pain in adults.

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Note

A.2.4 Etiological and prognostic factors

Literature

Search

In order to answer the clinical question, a systematic search was conducted for existing systematic reviews, possibly as part of an evidence-based guideline (see A1 'Introduction'), and three sources were selected that describe etiological and prognostic factors: the KNGF Guideline on Low Back Pain from 2013 (KNGF 2013), the NHG Standard on Non-specific Low Back Pain (NHG Guideline Panel for the Standard on Non-specific Low Back Pain 2017) and part 1 of the Lancet series (Hartvigsen 2018). Because no systematic search was conducted for the NHG Standard on Non-specific Low Back Pain (NHG Guideline Panel for the Standard on Non-specific Low Back Pain 2017) and part 1 of the Lancet series (Hartvigsen 2018), the core group conducted an additional systematic search in PubMed on 23 July 2019 for systematic reviews about etiological and/or prognostic factors for persistent low back pain that were published after the 2013 KNGF Guideline on Low Back Pain (see appendix A.2.4-1 for the search rationale).
The search yielded 1,126 hits; 1,060 articles were excluded based on title and abstract. Of the remaining 66 articles, the entire text was assessed. Ultimately, eight articles were included; etiological factors were studied in three of these articles (Da Silva 2017; Janwantanakul 2012; Pinheiro 2016), prognostic factors in four articles (Hallegraeff 2012; Oliveira 2019; Steenstra 2017; Verkerk 2012) and etiological and prognostic factors in one article (Campbell 2013). The table below lists the selection criteria of the search.

Selection criteria for the search for literature on etiological and prognostic factors for low back pain

Type of studies	Systematic review published in English or Dutch starting in 2012. **Exclusion:** literature review of primarily cross-sectional studies and literature review with a very limited scope (e.g. searches aimed at only one or two journals or with a focus on MRI findings).
Type of patients	Patients with low back pain with or without sciatica, without important warning signs (see A.1 'Introduction') **Exclusion:** systematic reviews that focus on specific populations, such as nurses, or on populations that fell outside of the inclusion criteria (e.g. postlumbar hernia patients and musculoskeletal pain).

Type of patients (continuation)	**Etiological factors: Participants have no complaints at inclusion.** **Prognostic factors:** Participants have complaints at inclusion.
Type of intervention	Not applicable
Type of comparison	Not applicable
Type of outcome	Etiological factors: Onset of low back pain (an initial episode or a relapse). Prognostic factors: persistent symptoms; pain or limitations in physical functioning or limitations in resuming work that last longer then three months.
Type of timeline	Follow-up of ≥3 months

Selection process for etiological and prognostic factors

The results were descriptively incorporated based on a narrative synthesis. The etiological and prognostic factors to be included in the guideline were selected based on consensus, with the following components having been assessed:

- The number of studies included in the systematic review that were relevant for the risk factor.
- The unequivocal nature of the burden of proof: Do the systematic reviews yield the same results or are the results conflicting?
- The association: Are the results statistically significant and/or clinically relevant? And
- The applicability: Does the factor constitute a treatable trait for the treatment of the physical therapist or exercise therapist and can the factor be properly assessed?

Considerations

Etiological factors

See the table in appendix A.2.4-2 for the etiological factors that were assessed and the results of the selection process.

The following risk factors of the onset of first-time back pain or recurring back pain were selected by the guideline panel to be included in the guideline based on consensus: 'previous episodes of low back pain' (Da Silva 2017; Hestbaek 2003; Janwantanakul 2012; Taylor 2014), 'overweight and obesity' (Ferreira 2013; Shiri 2010a; Zhang 2018), 'smoking' (Ferreira 2013; Shiri 2016, 2010b), 'co-morbidity' (Ferreira 2013), 'depression' (Pinheiro 2016), 'a high degree of physical load at work' (Heneweer 2011; Janwantanakul 2012; Lang 2012), 'a high degree of mental load at work' (Lang 2012), 'little social support at work' (Campbell 2013; Lang 2012), 'few options to independently fulfil work tasks' (Lang 2012), 'little job security' (Lang 2012) and 'very monotonous work' (Lang 2012).

Prognostic factors for persistent complaints

See the table in appendix A.2.4-2 for the prognostic factors that were assessed and the results of the selection process. The following prognostic factors were selected by the guideline panel for inclusion in the guideline: 'previous episodes of low back pain' (Chou 2010; Kent 2008), 'a high degree of limitations in activities' (Chou 2010; Hayden 2009, 2010; Kent 2008; Steenstra 2017), 'pain in the leg or sciatica' (Chou 2010; Hayden 2009, 2010; Kent 2008; Steenstra 2017; Verkerk 2012), 'high intensity of pain' (Chou 2010; Kent 2008; Steenstra 2017; Verkerk 2012), 'bad general health status or quality of life' (Chou 2010; Hayden 2009, 2010; Kent 2008; Ramond 2011; Steenstra 2017),

'psychological and psychosocial stress' (Hayden 2009, 2010; Kent 2008; Ramond 2011), 'pain-related fear of movement' (Chou 2010; Kent 2008; Ramond 2011;
Verkerk 2012; Wertli 2014b), 'feelings/symptoms of depression' (Hayden 2009; Hayden 2010; Kent 2008; Pinheiro 2016; Ramond 2011; Steenstra 2017; Verkerk 2012), 'passive coping' (Kent 2008; Ramond 2011), 'patient's negative expectations about recovery' (Hallegraeff 2012; Hayden 2009, 2010; Ramond 2011; Steenstra 2017) or 'catastrophisation' (Wertli 2014a), 'a high degree of physical load at work' (Chou 2010; Hayden 2009, 2010; Kent 2008; Steenstra 2017; Verkerk 2012), 'bad relationships with colleagues' (Hayden 2009, 2010) and 'diminished job satisfaction' (Chou 2010; Kent 2008; Ramond 2011; Steenstra 2017).

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Note A.3 Organisation of healthcare

Literature

Multidisciplinary collaboration

Disciplines that may be involved in the treatment include the following, for example: the physical therapist or exercise therapist, manual therapist, general practice-based nurse specialist for mental healthcare, primary care psychologist, occupational therapist, social worker, lifestyle coach and, in case of work-related problems, the company physician or insurance company physician. It appears that the quality of the healthcare and the organisational level of multidisciplinary collaboration in the primary care setting vary greatly, and in many cases there is room for improvement (Van Tulder 2010; Healthcare Institute of the Netherlands 2018). For example, Huijnen notes a lack of a mutual, uniform vision of pain, a large variation in content and duration

of care programmes, flawed communication among professional caregivers and fragmented healthcare financing. In addition, there are also various promising initiatives and developments in multidisciplinary healthcare whereby (para)medical professionals in the primary, secondary and tertiary care settings work closely together and new reimbursement structures are developed (Huijnen 2019).
The Sequenced Healthcare Guideline on Non-specific Low Back Pain (Van Tulder 2010), as well as the NHG Standard on Non-specific Low Back Pain (NHG Guideline Panel for the Standard on Non-specific Low Back Pain 2017) and the Chronic Pain Healthcare Standard (Perez 2017) argue for the organisation of a network and provide recommendations for cooperation and communication in multidisciplinary collaboration. Suggestions are also offered for local (institutional) or regional protocols and/or transmural healthcare agreements. In such a network, a back team coordinator will be hired to coordinate the multidisciplinary collaboration within the network and also be the point of contact for patients and involved healthcare providers. Who will fulfil the role of coordinator regarding the care of patients with chronic low back pain will be decided at the local or regional level. Decisive for this is the availability of a healthcare provider who has the required expertise for this. This healthcare provider then acts as an intermediary between patients and healthcare providers. The composition and working method of the network depends on the availability and expertise of the various healthcare providers in the respective field.
Within the network the recommendations of the sequenced healthcare guideline are translated into agreements about diagnostics and treatment, work resumption and about collaboration and communication (so about referrals and back referrals, mutual information exchange, and about guidance and information and advice for patients).

The rehabilitation physician has final responsibility for specialised medical rehabilitation. In addition to the rehabilitation physician, a BIG-registered psychologist and/or social worker and a number of paramedical professionals who are specialised in helping patients with chronic pain should ideally also be involved (Köke 2005). The composition of a rehabilitation team can differ somewhat per patient and per treatment location. Specialised medical rehabilitation is aimed at influenceable pain-sustaining factors. There is emphasis on pain education and coping with pain and stress. The patient's (physical and mental) load pattern is typically treated with graded activity, relaxation exercises and time management. In addition to cognitive behavioural therapy, Acceptance and Commitment Therapy (ACT) is being increasingly applied as psychological treatment intervention. For work-related problems, customised reintegration and guidance is offered or organisations are referred to that deal specifically with this, such as occupational health and safety agencies and reintegration companies (Central Supervisory Body [Centraal BegeleidingsOrgaan] 2014).
Two recent systematic reviews concluded that multidisciplinary treatment that is based on the biopsychosocial model is more effective for pain alleviation, functionality improvement and work resumption compared to monodisciplinary treatment (Kamper 2014; Salathe 2018). Multidisciplinary treatment was defined in these reviews as treatment involving multiple disciplines and with the treatment not only focusing on physical aspects but also on psychological and/or social aspects. However, the effects were not significant, and multidisciplinary treatment is expensive as well. Referring a patient to a multidisciplinary treatment team should therefore be carefully considered.

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Note B.1.1 Medical history taking

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Note B.1.2 Physical examination

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Note B.1.3 Red flags

Literature

In the primary care setting, the prevalence of warning signs in patients with low back pain is high, but the prevalence of serious specific conditions (red flag) is low. In an Australian study, 1,172 patients with acute low back pain (<2 weeks) were followed for one year in the primary care setting (Henschke 2009). Most patients (80.4%) had at least one warning sign, while the prevalence of a serious pathology was low (0.9%; fracture *n* = 8, infection *n* = 2, cauda equina syndrome *n* = 1). In the secondary and tertiary care setting, the prevalence of specific conditions is higher, but here too the diagnostic value of most warning signs was limited. In an American study, a retrospective analysis was conducted on the data of 9,940 patients with low back pain (with or without leg pain) who were treated in a specialised multidisciplinary spine clinic (Premkumar 2018). Most patients (92.6%) had at least one warning sign. In total, 8.3% of the patients were diagnosed with a serious pathology (fracture 5.6%, malignancy 1.6%, infection 1.2% and cauda equina syndrome 0.4%). The authors concluded that the absence of warning signs in general did not decrease the possible presence of a serious pathology. Most patients with a spinal malignancy (64%) did not have any warning signs, such as a history of cancer, inexplicable weight loss, night-time pain or over 50 or 70 years of age.

In a retrospective study, Tsjang (2019) investigated in a tertiary care setting (*n* = 500) the diagnostic value of warning signs for being able to prove fractures, malignancy, infections and cauda equina syndrome. The sensitivity and specificity turned out to be low for nearly all warning signs. The warning sign with the highest accuracy for the malignancy diagnosis was a history of cancer (sensitivity 0.75 [95% CI 0.53 to 0.90], specificity 0.79 [95% CI 0.75 to 0.82]). A fracture was best predicted by the presence of at least one of the following warning signs: osteoporosis, use of steroids and trauma (sensitivity 0.59 [95% CI 0.44 to 0.72], specificity 0.65 [95% CI 0.60 to 0.69]). Finucane (2020) recently published a framework whereby a synthesis was made of existing evidence and international expert consensus. The framework focuses on cauda equina syndrome, fractures, malignancy and infections and offers clinicians examination and treatment tools. An overview of the incidence and point prevalence of the four conditions mentions the following data. The point prevalence for cauda equina syndrome as a cause of low back pain is estimated to be 0.04% in the primary care setting and 0.4% in the tertiary care setting. The syndrome occurs as a complication in about 2% of patients with a lumbar disc herniation. The incidence after a lumbar operation is estimated to be between 0.08 and 0.2%. The point prevalence of osteoporotic fractures as a cause of low back pain varies from 0.7% to 4.5% in the primary care setting to 6.5% in the emergency room. Just like metastases, osteoporotic fractures primarily occur in the

thoracic spine (70%) and to a lesser degree in the lumbar (20%) and cervical spine (10%). The point prevalence of a traumatic fracture as a cause of low back pain is estimated at <1% in the primary care setting. The point prevalence of malignancies as a cause of low back pain varies from 0.0 to 0.7% in the primary care setting, is 0.1% in the emergency room and is 1.6% in the tertiary care setting. The point prevalence of infections as a cause of low back pain is estimated to be 0.01% in the primary care setting and 1.2% in the tertiary care setting.

International guidelines

There is no consensus in international guidelines about the minimum warning signs based on which patients with low back pain should be screened, or about the question of which combinations of symptoms justify specialised examination. Verhagen (2016) found 46 different warning signs in 16 guidelines that could indicate a malignancy, fracture, cauda equina syndrome or infection. Parreira (2019) found 12 different warning signs in 78 guidelines for the possible presence of fractures. Both research groups concluded that there was hardly consensus and that most recommendations were not based on scientific evidence, nor were they supported by clinically relevant data.

Considerations

The guideline panel believes it is important to screen patients with low back pain for warning signs and red flags in order to decrease the chance of missing serious pathology. When assessing the relevancy of warning signs, the therapist always includes information from the medical history taking and the physical examination.

The guideline panel concludes that the presence of a single warning sign does not necessarily need to point to a specific cause, and that there are indications that specific combinations of various warning signs increase the probability of a specific condition.

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Note B.2 Indications and treatment profiles

Literature

A recent literature review of the most important recommendations in guidelines for primary care describes two ways of giving direction to the treatment: 'stepped-care' and 'stratified care' (Almeida 2018). Linton (2018) adds a third way – 'matched care' – and provides an overview of the assumptions that underlie the three models and their advantages and limitations.

A brief description of the three models follows.

With the stepped-care approach, one begins with the simplest and least intensive treatment and then switches to more complex and intensive treatment options when the simple treatments are not successful. The most important assumptions are that low back pain is not impacted by existing psychosocial factors and that a wait-and-see policy is cost effective. The main limitations that are mentioned are that the stepped-care model ignores the complexity

of the complaints and may cause a delay in assigning the correct treatment to patients with an increased risk of persistent complaints. The stepped-care approach assumes a favourable natural course of the back pain, whereby patients with short-term complaints (acute low back pain; <6 weeks) would recover faster than patients with longer-lasting complaints (subacute low back pain; 6-12 weeks or chronic low back pain; >12 weeks).

- With the stratified-care approach, patients are grouped based on established risk factors, with a congruent intensity of the intervention. The stratified-care approach is intended to offer more intensive treatment to patients who need it, while patients with a low risk generally recover with minimal guidance. The most important assumption is that risk factors can be identified, that risk factors are relatively stable and that a larger number of risk factors are accompanied by an increased risk of persistent complaints. The most important limitation of stratified care is that the treatment based on risk stratification is not always congruent with the patient's individual risk profile.
- With the matched-care approach, the treatment is also based on risk factors, but different from a stratified approach, whereby the treatment modules are more or less uniform, the treatment is adapted to the individual patient's risk profile. The assumptions for matched care largely correspond to those of stratified care, with the addition that there are specific treatments for risk factors and that targeted treatment increases the efficiency of the treatment. The most important limitation of matched care is that the identification of risks for forming profiles is still in development. In addition, the matched care model is more complex to implement than the other two models.

There is as yet nothing known about the (cost) effectiveness based on which the one model should be chosen over the other.
The guideline of the National Institute for Health and Care Excellence (NICE) and the KCE guidelines employ a stratified-care approach, and the NHG Standard on Non-specific Low Back Pain employs a stepped-care approach (NHG Guideline Panel for the Standard on Non-specific Low Back Pain 2017).

Considerations

The guideline panel recognises the need for a classification into treatment profiles in order to offer practicing physical therapists and exercise therapists tools for guiding the therapy and facilitating the clinical decision-making process. The guideline panel believes that the risk of persistent low back pain can play an important role here. Someone with short-term complaints may have an increased risk of persistent complaints, for which more intensive treatment is immediately indicated. Evaluation of the risk of persistent low back pain can offer valuable information for the timely initiation of the correct treatment strategy. The guideline panel is aware that there is still a lot of uncertainty about the extent to which prognostic factors can predict the risk of persistent low back pain and what the value is for the individual patient. However, the guideline panel assumes that if a factor is dominant, or if there is a combination of factors, this impedes the chance of recovery. The guideline panel also believes that patients with low back pain can best be assigned to treatment profiles based on an evaluation of the risk of persistent complaints using the most important prognostic factors for persistent low back pain.
The guideline panel finds it important to assess the patient's individual risk profile because the clinical decision-making process can be adjusted based on this.
The guideline panel considers that there is a low risk of persistent complaints if there are no dominant prognostic factors for delayed recovery, a moderate risk of persistent low back pain if

there are some non-dominant prognostic factors for delayed recovery and a high risk of persistent low back pain if there are dominant prognostic factors for delayed recovery.
Psychosocial prognostic factors play an important role in the classification into treatment profiles. If psychosocial prognostic factors are dominant in the therapist's estimation and have a sustained and negative impact on movement-related functioning, the patient is assigned to treatment profile 3. In such cases, behaviour-oriented treatment is considered (see C.3 'Behaviour-oriented treatment').
The guideline panel believes that the classification into treatment profiles, which in its current form is based on the individual evaluation by the physical therapist and exercise therapist, requires further development. The differentiation between the treatment profiles in its current form should be operationalised more explicitly in order to minimise individual variation in classification between therapists. In order to shape this, the guideline panel has formulated knowledge gaps on which scientific research can focus. These knowledge gaps will be published with the guideline.

Course and duration of low back pain

Within this guideline, a decision was made to have the risk of persistent complaints of low back pain be decisive for the classification into treatment profiles. The course of the low back pain therefore no longer plays a role in deciding the treatment profile at the start of the treatment. Determining the treatment profile based on the course has its limitations, because you can only determine whether there is an abnormal course after some time has passed, meaning that a wait-and-see policy would have to be pursued in the beginning phase after the onset of complaints. There is also some evidence that there are no clinically relevant differences in the extent of recovery on pain, physical functioning, quality of life, anxiety and depression for patients with low back pain with a different duration of complaints at baseline (Jess 2018).
We speak of an abnormal course and delayed recovery when there has been no significant increase in activities and decrease in participation problems for three weeks (KNGF 2013). The wait-and-see policy runs counter to the theoretical construct of the current guideline, where the emphasis is on identifying risk factors for delayed recovery. A wait-and-see policy can cause a delay in initiating the correct treatment for those with an increased risk of persistent complaints. In contrast, the guideline panel recognises that an abnormal course of the back pain is a sign to reconsider the classification into the treatment profile and the associated treatment during the treatment course. An abnormal course of the complaints is therefore designated within the current guideline as an indication for re-evaluating the risk of persistent complaints. The treatment strategy can be modified based on the re-evaluation.
Another classification that is often used is classification based on the duration of the complaints: acute low back pain (<6 weeks), subacute low back pain (6-12 weeks) and chronic low back pain (>12 weeks). Determining the treatment profile based on the duration of the complaints also has its limitations, because this classification does not take into account the large variation in symptoms and pain courses that are reported by people with low back pain and does not properly discriminate between chronic pain and relapsing low back pain. The traditional classification based on the duration of the complaints was therefore contested by the determination that low back pain is often a long-lasting condition with a variable course (Dunn 2013; Hartvigsen 2018; Kongsted 2016); some patients recover and some patients have persistent, severe low back pain (Kongsted 2016). The duration of the complaints has not been designated as an important prognostic factor within this guideline. There is conflicting evidence for the duration of the

complaints as a prognostic factor for persistent complaints of low back pain (see A.2.4 'Etiological and prognostic factors'). A longer duration of the back pain is associated with a worse outcome in one of the two systematic reviews (Hayden 2009). This finding does not mean, however, that complaints lasting more than 12 weeks is the same as 'short-term low back pain that lasts longer'. Compared to short-term low back pain, with chronic pain there is a bigger chance that the experienced pain is the result of a complex interplay of physical, psychological and social factors. Chronic pain can cause permanent changes in the pain system, for example, including maladaptive neuroplastic changes in the somatosensory system (e.g. hyperactivity of the nociceptive system) and the pain memory (pain persists even though the cause has disappeared) (Jonckheer 2017). The guideline panel believes that the duration of the complaints is an important patient characteristic that should be assessed during the medical history taking.

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Note B.2.1 Classification systems

Literature

To answer the clinical question, a systematic literature analysis was carried out on the following research questions (PICO):

- Treatment-based Classification System (TCS)
  1. What are the desirable and undesirable effects (O) of the TCS (I) versus no stratified treatment (C) in patients with low back pain with or without sciatica, without important warning signs (P)?
- Classification Based Cognitive Functional Therapy (CB-CFT)
  2. What are the desirable and undesirable effects (O) of CB-CFT (I) versus no stratified treatment (C) in patients with low back pain with or without sciatica, without important warning signs (P)?
- Treatment based on classification by means of the STarT Back Screening Tool (SBST)
  3. What are the desirable and undesirable effects (O) of treatment according to the SBST (I) versus no stratified treatment (C) in patients with low back pain with or without sciatica, without important warning signs (P)?

Based on the literature, the guideline panel selected 'quality of life', 'pain', and 'physical functioning' as crucial outcome measures and 'work resumption' as an important outcome measure (Chiarotto 2015; ICHOM Working Group Members for Low Back Pain 2017; Verburg 2019). Undesirable effects are all negative effects that may be related to the intervention (e.g. increased pain and/or limitations in physical functioning, or pain and/or limitations in physical functioning of a type other than the kind for which one initially sought help, occurring immediately after the intervention).

Search

The literature review was conducted in a hierarchical manner; the search first focused on existing evidence-based guidelines. Using an orientating search for evidence-based guidelines in PubMed on 2 May 2019, the guideline of the National Institute for Health and Care Excellence (NICE) was

identified. This guideline is of high methodological quality and uses a corresponding clinical question (De Campos 2017): 'What is the clinical and cost effectiveness of stratifying management of non-specific low back pain or sciatica according to outcome of a risk assessment tool/ questionnaire?'
To answer this question, the NICE searched in MEDLINE, Embase and the Cochrane Library up to 15 December 2015, based on which six studies were included (Apeldoorn 2012b, Beneciuk 2015; Foster 2014; Fritz 2003; Hill 2011; Vibe Fersum 2013). We reviewed these studies based on the selection criteria that we formulated beforehand within the scope of our three research questions. See the following table.

Selection criteria for the search on literature about stratified treatment

Type of studies	Randomised controlled study published in English or Dutch
Type of patients	Adults with low back pain with or without sciatica, without important warning signs (see A.1 'Introduction')
Type of intervention	Targeted treatment after stratification pursuant to the TCS, CB-CFT or SBST
Type of comparison	The usual healthcare, no stratified treatment
Type of outcome	**Desirable:** - **Crucial:** quality of life, pain, physical functioning **Important:** work-related outcomes **Undesirable:** all negative effects that might be related to the intervention
Type of timeline	Short (≤4 months) and/or long (>4 months) term. In the event of multiple measurement points, the measurement point that is closest to this time indication is included.

One study included by the NICE concerned an observational cohort and was therefore excluded (Foster 2014).
On 8 May 2019, an information specialist (J.W. Schoones, Leiden University Medical Centre) conducted a systematic search in PubMed, MEDLINE, Embase, Emcare, Web of Science and the Cochrane Library for updating of the NICE guideline (see appendix B.2.1-6 for the search rationale). This search produced 268 unique hits. After screening of the title and the abstract based on the inclusion criteria, 253 articles were excluded. The complete article was screened for 14 articles; ultimately, the search yielded one additional study (Cherkin 2018). The total number of studies in this literature analysis hence amounts to six (Apeldoorn 2012b; Beneciuk 2015; Cherkin 2018; Fritz 2003; Hill 2011; Vibe Fersum 2013). See appendix B.2.1-1 for the flowchart of the inclusion process. The articles that were excluded based on the complete text and the reason for the exclusion are listed in appendix B.2.1-2 (Balasubramaniam 2016; Barone 2018; Bello 2017, 2018; Beneciuk 2015; Cherkin 2016; Morso 2018; Murphy 2016; Ng 2015; O'Keeffe 2015; Riis 2016; Vibe Fersum 2019; Whitehurst 2015).

Characteristics of the included studies

The characteristics of the included studies are provided in appendix B.2.1-3. The six included studies included a total of 2,991 patients with low back pain. The average age of the patients varied between 37 and 50 years, and the percentage of women was 38% to 64%. The duration of

the complaints varied from one day to more than five years, and the percentage of patients with sciatica into the legs varied from 18% to 63% (2 studies did not report data about the percentage of patients with sciatica into the legs).
Two studies (Apeldoorn 2012b; Fritz 2003) described the effectiveness of stratified treatment based on the TCS of Hicks and Delitto (1995). In the study by Fritz, the intervention entailed mobilisation, manipulation techniques, active range-of-motion exercises, strength training of the trunk and mechanical traction (treatment period not specified), and in the study by Apeldoorn it entailed lumbar manipulation, stabilisation exercises or direction-specific exercises during at least four weeks.
One study (Vibe Fersum 2013) described the effectiveness of stratified treatment based on the CB-CFT by O'Sullivan (2005). The CB-CFT is based on the biopsychosocial model and has a cognitive component, a component with exercises that are aimed at functional integration of activities in daily life, and a physical activity programme aimed at 'movement classification'.
Three studies (Beneciuk 2015; Cherkin 2018; Hill 2011) described the effectiveness of stratified treatment based on the SBST of Hill (2008) in comparison with treatment without risk stratification. The SBST group also received additional treatment: the low-risk group received advice and pain medication, the medium-risk group received regular evidence-based physical therapy and the high-risk group received psychosocial therapy.

Individual study quality (RoB)

The design and execution of the individual studies (risk of bias, RoB) was assessed by NS with the help of the Cochrane Risk-of-Bias tool (Higgins 2011a). The opinion of the various items was discussed with the AA and RO, after which consensus was achieved. An overview of the study quality assessment (RoB) per study is provided in appendix B.2.1-4.

Effectiveness and evidentiary value of the TCS versus no risk stratification per outcome measure

The effect of the treatment based on the TCS was compared in two studies to treatment without risk stratification (Apeldoorn 2012b, Fritz 2003).
An overview of the results in the short term and long term that could be pooled is depicted in the following tables.

GRADE evidence profile of the studies on treatment with risk stratification according to the TCS versus treatment without risk stratification in the short term (≤4 months) (taken from the NICE guideline)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	Type of outcome measure
	Study design and execution (RoB)[1]	Inconsistency	Indirectness	Imprecision[2]	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Quality of life (SF-36; PCS 0-100)										
1	very severe	not severe	not severe	very severe	not determined	37	41	MD 6.2 (-8.74; 21.14)	very low	crucial
Quality of life (SF-36; PCS 0-100)										
1	very severe	not severe	not severe	very severe	not determined	37	41	MD 1.6 (-13.34; 16.54)	very low	crucial

Pain (NPRS; 0–10)										
1	very severe	not severe	not severe	severe	not determined	74	82	MD −0.49 (−1.34; 0.36)	very low	crucial
Physical functioning (ODI 0–100)										
2	very severe	not severe	not severe	not severe	not determined	111	123	MD −1.16 (−5.13; 2.82)	very low	crucial
Work-related outcomes (number of patients with work restrictions (not further operationalised))[3]										
1	very severe	not severe	not severe	very severe	not determined	7 / 41	15 / 37	RR 0.42 (0.19; 0.92)	very low	important
Undesirable effects[3]										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RoB = risk of bias; RR = risk ratio; SF-36 = 36-Item Short Form Health Survey.
[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. [3] This outcome measure was not included by NICE, but was added in consultation with the guideline panel.
Note: A higher score corresponds to less pain and a higher level of physical functioning. A positive MD represents an advantage for the intervention group.

GRADE evidence profile of the studies on treatment with risk stratification according to the TCS versus treatment without risk stratification in the long term (> 4 months) (taken from the NICE guideline)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	Type of outcome measure
	Study design and execution (RoB)[1]	Inconsistency	Indirectness	Imprecision[2]	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Quality of life (SF-36; PCS 0–100)										
2	very severe	not severe	not severe	not severe	not determined	111	123	MD −0.59 (−3.7; 2.52)	low	crucial
Quality of life (SF-36; PCS 0–100)										
2	very severe	not severe	not severe	not severe	not determined	111	123	MD 0.94 (−2.24; 4.12 higher)	low	crucial
Pain (ODI 0–10)										
1	very severe	not severe	not severe	severe	not determined	74	82	MD 0.13 (−0.83; 1.09)	very low	crucial
Physical functioning (NPRS; 0–100)										
2	very severe	not severe	not severe	not severe	not determined	111	123	MD 0.23 (−4.09; 4.54 higher)	low	crucial

Work-related outcomes (number of patients that missed at least 1 day of work due to back pain)[3]										
1	very severe	not severe	not severe	very severe	not determined	6 / 35	11 / 32	RR 0.50 higher (-0.21; 1.19)	very low	important
Undesirable effects[3]										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RoB = risk of bias; RR = risk ratio; SF-36 = 36-Item Short Form Health Survey.
[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. [3] This outcome measure was not included by NICE, but was added in consultation with the guideline panel.
Note: A higher score corresponds to less pain and a higher level of physical functioning. A positive MD represents an advantage for the intervention group.

Effectiveness and evidentiary value of the CB-CFT versus treatment without risk stratification

The effect of the CB-CFT compared to treatment without risk stratification is described in one study (Vibe Fersum 2013).

An overview of the results in the short term and long term that could be pooled is depicted in the following tables.

GRADE evidence profile of the studies on treatment with risk stratification according to the CB-CFT versus treatment without risk stratification in the short term (≤4 months) (taken from the NICE guideline)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	Type of outcome measure
	Study design and execution (RoB)[1]	Inconsistency	Indirectness	Imprecision[2]	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Quality of life; PCS										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	crucial
Quality of life; MCS										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	crucial
Pain (VAS, 0-10)										
1	very severe	not severe	not severe	severe	not determined	51	43	MD -2.1 (-2.83; -1.37)	very low	crucial
Physical functioning (ODI 0-100)										
1	very severe	not severe	not severe	severe	not determined	51	43	MD -10,9 (-13.94; -7.86)	very low	crucial
Work-related outcomes[3]										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	important
Undesirable effects[3]										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; PCS = Physical Component Score; MCS = Mental Component Score; MD = mean difference; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; RCTs = randomized controlled trials; RoB = risk of bias; VAS = Visual Analogue Scale.
[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. [3] This outcome measure was not included by NICE, but was added in consultation with the guideline panel.
Note: A higher score corresponds to less pain and a higher level of physical functioning. A positive MD represents an advantage for the intervention group.

GRADE evidence profile of the studies on treatment with risk stratification according to the CB-CFT versus treatment without risk stratification in the long term (> 4 months) (taken from the NICE guideline)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	Type of outcome measure
	Study design and execution (RoB)[1]	Inconsistency	Indirectness	Imprecision[2]	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Quality of life; PCS										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	crucial
Quality of life; MCS										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	crucial
Pain (VAS, 0-10)										
1	very severe	not severe	not severe	severe	not determined	51	43	MD -1.5 (-2.33; -0.67)	very low	crucial
Physical functioning (ODI 0-100)										
1	very severe	not severe	not severe	severe	not determined	51	43	MD -9,8 (-14.21; -5.39)	very low	crucial
Work-related outcomes (number of patients that missed at least 1 day of work due to back pain)[3]										
1	very severe	not severe	not severe	severe	not determined	51	43	RR 0.60 (0.37; 0.96)	very low	important
Undesirable effects[3]										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; PCS = Pain Component Score; MCS = Mental Component Score; MD = mean difference; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; RCTs = randomized controlled trials; RR = risk ratio; RoB = risk of bias; VAS = Visual Analogue Scale.
[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. [3] This outcome measure was not included by NICE, but was added in consultation with the guideline panel.
Note: A higher score corresponds to less pain and a higher level of physical functioning. A positive MD represents an advantage for the intervention group.

Effectiveness and evidentiary value of the SBST versus treatment without risk stratification

The effect of stratification with SBST compared to usual care (treatment without risk stratification) is described in three studies (Beneciuk 2015; Cherkin 2018; Hill 2011).

An overview of the results in the short term and long term that could be pooled is depicted in the following tables.

GRADE evidence profile of the studies on treatment with risk stratification according to the SBST versus treatment without risk stratification in the short term (≤4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	Type of outcome measure
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision[2]	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Quality of life (SF-12, PCS 0-100)										
1	severe[1]	not severe	not severe	not severe	not determined	568	283	MD 2.30 (0.42; 4.16)	moderate	crucial
Quality of life (SF-12, MCS 0-100)										
1	severe[1]	not severe	not severe	not severe	not determined	568	283	MD 0.00 (-1.58; 1.58)	moderate	crucial
Pain (VAS/NPRS, 0-10)[3]										
3	severe[1]	not severe	not severe	not severe	not determined	1339	1196	MD -0.54 (-0.77; -0.31)	moderate	crucial
Physical functioning (ODI RMDQ 0-100/0-24)										
3	severe[1]	not severe	not severe	not severe	not determined	1339	1196	SMD -0.15 (-0.23; -0.07)	moderate	crucial
Work-related outcomes (number of absenteeism hours due to back pain)										
1	very severe[2]	not severe	not severe	severe[4]	not determined	350	461	MD 1.37 (-0.13; 2.88)	very low	important
Undesirable effects (single serious morbidity or event)										
1	very severe[2]	not severe	severe[3]	not severe	not determined	568	283	0	very low	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RMDQ = Roland Morris Low Back Pain and Disability Questionnaire; RoB = risk of bias; SF-12 = 12-Item Short Form Health Survey; SMD = standardized mean difference; VAS = Visual Analogue Scale.

[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 2 levels because more than 50% of participants comes from studies with a selection and performance bias. [3] Down-graded by 1 level due to the varied and imprecise descriptions of the measurement methods. [4] Down-graded by 1 level because the 95% CI exceeds no effect and a clinically relevant effect (broad confidence interval).

Note: A higher score corresponds to less pain and a higher level of physical functioning. A positive MD represents an advantage for the intervention group.

GRADE evidence profile of the studies on treatment based on SBST versus treatment without risk stratification in the long term (> 4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	Type of outcome measure
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision[2]	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Quality of life (SF-12, PCS 0-100)										
1	severe[1]	not severe	not severe	not severe	not determined	568	283	MD 2.30 (0.73; 3.87)	moderate	crucial
Quality of life (SF-12, MCS 0-100)										
1	severe[1]	not severe	not severe	not severe	not determined	568	283	MD 0.50 (-1.39; 2.39)	moderate	crucial
Pain (VAS/NPRS, 0-10)										
2	severe[1]	not severe	not severe	not severe	not determined	1258	1147	MD -0.02 (-0.28; -0.24)	moderate	crucial
Physical functioning (RMDQ, 0-24)										
2	severe[1]	not severe	not severe	not severe	not determined	1258	1147	MD -0.12 (-0.69; -0.16)	moderate	crucial
Physical functioning (RMDQ, 0-24)										
1	very severe[2]	not severe	not severe	severe[4]	not determined	896	721	MD -7.80 (-12.25; -3.35) (*n* = 851; number of absenteeism days) MD 1.37 (-0.13; 2.88) (*n* = 766; number of absenteeism days)	very low	important
Undesirable effects (single serious morbidity or event)										
1	very severe[2]	not severe	severe[3]	not severe	not determined	568	283	0	very low	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RMDQ = Roland Morris Low Back Pain and Disability Questionnaire; RoB = risk of bias; SF-12 = 12-Item Short Form Health Survey; SMD = standardized mean difference; VAS = Visual Analogue Scale.

[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 2 levels because more than 50% of participants comes from studies with a selection and performance bias. [3] Down-graded by 1 level due to the varied and imprecise descriptions of the measurement methods. [4] Down-graded by 1 level because the 95% CI exceeds no effect and a clinically relevant effect (broad confidence interval).

Note: A higher score corresponds to less pain and a higher level of physical functioning. A positive MD represents an advantage for the intervention group.

Considerations

To answer the clinical question, other considerations were also included in the literature to recommendation process in addition to the literature. Together they determine the direction and strength of the recommendation. The assessment of considerations and the explanation per classification system are provided in appendix B.2.1-5.

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Note B.3 Measurement instruments

Literature

This question was answered by describing the recommended and optional measurement instruments that can be used during the diagnostic process. The Clinimetric Framework for Evidence-based Products was used for this (KNGF 2016).
The framework concerns a step-by-step plan with which measurement instruments can be selected in a goal-oriented manner in eight steps by means of an iterative process.

- **Step 1** What do you want to measure?
- **Step 2** Why do you want to measure?
- **Step 3** What kind of measurement instrument do you want to use to measure?
- **Step 4** How can you find a measurement instrument?
- **Step 5** What is the practicability?
- **Step 6** What is the clinimetric quality?
- **Step 7** Are standard values available?
- **Step 8** How do you calculate and interpret the data?

Then a description is provided that justifies the choice of the measurement instruments.

When answering the clinical question, scientific literature was consulted regarding the development of a set of core measurement instruments for patients with low back pain based on three initiatives (Chiarotto 2018a, ICHOM Working Group Members for Low Back Pain 2017; Verburg 2019). All three initiatives were based on a literature review and a formal decision-making and

consensus process with patients, healthcare providers, researchers, policy-makers and health insurance companies, whereby the initiative by Chiarotto (Chiarotto 2018a) primarily had the goal of standardising the use of measurement instruments in scientific research, and both initiatives were aimed at the use of measurement instruments in practice (ICHOM Working Group Members for Low Back Pain 2017; Verburg 2019).
The guideline differentiates between recommended measurement instruments and optional measurement instruments. It is recommended to use the first set in all patients, unless there is a special reason not to use a specific measurement instrument for a patient. Optional measurement instruments are used if there is a special reason to do so for a patient.

Literature for step 1 – What do you want to measure?

There is consensus between the sets about the measurement domains 'pain intensity' and 'physical functioning'. In two sets, 'health-related quality of life' is designated as a relevant domain (Chiarotto 2015; ICHOM Working Group Members for Low Back Pain 2017); the other set is aimed at a more global evaluation of the recovery from complaints experienced by the patient (Verburg 2019). In one of the three sets, the recommendation is to assess the risk of persistent complaints (Verburg 2019). The guideline panel prioritised measuring the domains 'pain', 'physical functioning' and 'activities and participation' as domains on which to focus the recommended measurement instruments.
The following table compares the selected domains and measurement instruments within the various initiatives.

Core set of measurement instruments of the various initiatives

Domain	(Chiarotto 2018a)	(Verburg 2019)	(ICHOM Working Group Members for Low Back Pain 2017)
pain	NPRS	NPRS	NPRS
physical functioning	ODI version 2.1a 24-item RMDQ	ODI* QBPDS PSC	ODI
health-related quality of life	SF12 10-item PROMIS Global Health form	not applicable	EQ-5D
experienced recovery	not applicable	GPE-DV	not applicable
risk of persistent symptoms	not applicable	SBST	not applicable

EQ-5D = EuroQol-5D; GPE-DV = Global Perceived Effect; NPRS = Numeric Pain Rating Scale; ODI = Oswestry Disability Index; PROMIS = Patient-Reported Outcomes Measurement Information System Global Health short form; PSC = Patient-Specific Complaints; QBPDS = Quebec Back Pain Disability Scale; RMDQ = Roland-Morris Disability Questionnaire; SBST = STarT Back Screening Tool; SF-12 = 12-Item Short Form Health Survey.
* The ODI was added as a pilot to enable comparison of the psychometric characteristics with the QBPDS.

Literature for step 2 – Why do you want to measure?

The primary goal of the measurements is diagnostics or to evaluate the treatment.

Literature for step 3 – What kind of measurement instrument do you want to use to measure?

The guideline panel opted to assess the specified domains using questionnaires, because these are used the most frequently in daily practice and scientific research, and questionnaires are practicable (see step 5). The guideline panel believes that questionnaires should ideally be combined with a performance or function test, but the guideline panel recognises that no solid instruments are available to satisfy this need.
To facilitate implementation of the guidelines, the KNGF Clinimetric Framework recommends assigning only one or a few measurement instruments to a domain in order to reduce the total number of recommended measurement instruments in a guideline (KNGF 2016).

Literature for step 4 – How can you find a measurement instrument?

The recommended and optional measurement instruments are freely available at www.meetinstrumentenzorg.nl.

Literature for step 5 – What is the practicability for the therapist and the patient?

This step has only been elaborated within the scope of this guideline for the recommended measurement instruments.

Pain

There is consensus among the three initiatives about the NPRS as a measurement instrument for measuring pain. The NPRS is easy to use. It does not take a lot of time to complete, it barely necessitates any additional expertise or experience on the part of the therapist and requires minimal effort by the patient. De NPRS is available for free for healthcare organisations; a licence is not necessary (ICHOM Working Group Members for Low Back Pain 2017). The practicability of the NPRS is deemed to be better than that of the VAS.

Physical functioning

There is no consensus among the initiatives about the question of which measurement instrument are best to measure the domain 'physical functioning', either the Oswestry Disability Index (ODI), the Roland-Morris Disability Questionnaire (RMDQ) or the Quebec Back Pain Disability Scale (QBPDS). The ODI consists of 10 items about the severity of pain, self-sufficiency, lifting, walking, sitting, standing, sleeping, sex life, social life and travel/transport, measured using a six-point scale (0 = 'no limitations' and 5 = 'the most limitations'). The total score with a range from 0 to 100 is measured by multiplying the total score of the items by a factor of 2 (a higher score corresponds to more limitations). The original version (Fairbank 1980) has been translated into Dutch (Van Hooff 2015). However, there are multiple versions of the ODI in circulation. In a modified version of the questionnaire, the (modified) Oswestry Low Back Pain Disability Questionnaire (Oswestry LBPDQ), the item about sex life has been replaced by an item about work/housework. There is no official Dutch translation of the Oswestry LBPDQ, and the psychometric characteristics of this questionnaire are still largely unknown. That is why, within the scope of this guideline, we assumed the original questionnaire (Fairbank 1980). The most recent version of the English questionnaire (which had not yet been translated when this guideline was developed) is 2.1b. However, the differences are not such that the Dutch translation of version 2.1a (Van Hooff 2015) would not be able to be

used until it has been updated to version 2.1b (see https://eprovide.mapi-trust.org/instruments/oswestry-disability-index#review_copy).
The RMDQ is a questionnaire with 24 items about physical functioning with a dichotomous scale (yes/no). The total score is the sum of all positively scored items and varies from 0 to 24 points. A higher score corresponds to more limitations. The original questionnaire and the translation are public. The original version (Roland 1983) was translated into Dutch by Van der Heijden (van der Heijden 1991; was not investigated further). There are different versions of the RMDQ. The recommendation is to use the RMDQ-24 with the addition 'due to my back or leg problems' (Smeets 2011).
The QBPDS has a questionnaire with over 20 items on bed rest, sitting and standing, walking, moving, bending and moving heavy objects, measured on a six-point scale (0 = 'no effort' and 5 = 'unable'). The total score is the sum of all items and varies from 0 to 100 points (0 = 'no limitations' and 100 = 'completely limited'). The original version (Kopec 1995) has been translated into Dutch (Schoppink 1996).
The ODI, RMDQ and QBPDS are easy to use. They take an average of 5 to 10 minutes to complete and there is almost no additional expertise or experience required on the part of the therapist. Completing the questionnaires does require some mental effort on the part of the patient.
The ODI and the QBPDS are freely available for clinicians, but downloading the original questionnaires requires a licence (ODI: see https://eprovide.mapi-trust.org/instruments/oswestry-disability-index; QBPDS: https://eprovide.mapi-trust.org/instruments/quebec-back-pain-disability-scale). There are licensing costs associated for IT companies, which may present an obstacle to incorporating the questionnaire in the electronic patient records. No permission is needed for using and reproducing the RMDQ, and there are no costs associated with its use (see http://www.rmdq.org/).

> The guideline panel estimates that the ODI, RMDQ and QBPDS are very practicable for therapists and patients. The RMDQ may be a bit more practicable than the ODI and the QBPDS, because no permission is required for its use.

Activities and participation in ADL

For the activities and participation in ADL domain, the guideline panel added the PSC to one of the sets of core measurement instruments (Verburg 2019). The PSC makes it possible to determine the functional status of the individual patient. The patient selects the three to five most important complaints with regard to physical activities. The patient scores the degree of impairment on a Numeric Pain Rating Scale (NPRS) from 0 to 10 (0 = 'no difficulties' and 10 = 'impossible'). The higher the total score, the more problems experienced when carrying out the activity. A list of activities is available for patients with low back pain as an aid at www.meetinstrumentenzorg.nl.
The PSC is easy to use. It does not take a lot of time to complete (Stevens 2013), barely necessitates any additional expertise or experience on the part of the therapist and requires minimal effort by the patient. De PSC is available for free for healthcare organisations; a licence is not necessary. This is an originally Dutch measurement instrument (Beurskens 1999).
The Patient-Specific Goal-setting method (PSG) (Stevens 2017a,b, 2018) is the updated version of the PSC. The PSG can be used as a method to set goals together with the patient, which better integrates goal-setting in THE therapeutic methodical approach. However, training is required to learn to properly apply the PSG, and almost no research has been done (yet) on the clinimetric

quality of the PSG. The guideline panel has therefore decided to include the PSC into the guideline as a recommended measurement instrument and to include the PSG as an alternative as one of the optional measurement instruments.

Literature for step 6 – What is the clinimetric quality of the recommended measurement instruments?

Pain

Despite the frequent use of the VAS and the NPRS, there is no evidence that clearly suggests that one of the two is superior to the other in patients with low back pain. Research of high methodological quality is needed in which the clinimetric quality of both instruments is compared to each other (Chiarotto 2019).
One constraint of the NPRS is that it can only be used to determine one dimension of pain, specifically pain intensity, one of the core sets of the instrument. This is hence the reason why this term is used in the guideline (Chiarotto 2019). For purposes of uniformity with the previous guideline, it was decided to evaluate the average pain intensity over the past 24 hours.

> The guideline panel agrees with the recommendation of an international panel of experts to complete the NPRS for average pain over the past 24 hours.

Physical functioning

For the physical functioning domain, there was no consensus among the initiatives about the selected instrument for the set with core measurement instruments. After this follows the assessment of the clinimetric quality of the three selected measurement instruments: the ODI, the RMDQ and the Quebec Back Pain Disability Scale (QBPDS).
A systematic review on the content and construct validity of the measurement instruments for physical functioning in patients with low back pain concludes that there is a low to very low evidentiary value for the content validity of the 16 examined measurement instruments, including the ODI and the QBPDS (Chiarotto 2018b). For the RMDQ-24, evidence of high quality was found for sufficient comprehensibility and for insufficient comprehensiveness, with the evidentiary value of the relevance being assessed as very low (Chiarotto 2018b). It was also determined that the RMDQ-24 does not measure unidimensionally; the results of the ODI and the QBPDS about the unidimensionality are inconsistent (Chiarotto 2018b).
A narrative literature review concludes that the ODI exhibits a high degree of internal consistency (Cronbach's alpha 0.71 to 0.87) and good test-retest reliability (intraclass correlation coefficient (ICC) 0.84, 95% CI 0.73 to 0.91). A measurement error of 4 to 6 was found (Smeets 2011). The reproducibility of the QBPDS is assessed in the same narrative literature review as follows: high degree of internal consistency (Cronbach's alpha 0.90); good test-retest reliability (ICC 0.92) and a measurement error ('minimum detectable change') of 0.84 (95% CI 0.73 to 0.91) (Smeets 2011). The reproducibility of the RMDQ is assessed as follows: high degree of internal consistency (Cronbach's alpha 0.84 to 0.96); moderate test-retest reliability (ICC 0.42-0.53) in a mixed population of acute, subacute and chronic low back pain and a measurement error (SEM) of 3.7 to 4.1.
A narrative literature review concludes that the ODI is responsive in detecting change (AUC > 0.76); conflicting results were found for the QBPDS and the RMDQ (Smeets 2011).

The guideline panel notes that based on validity, reproducibility and responsiveness, no clear preference can be stated for the ODI, RMDQ or QBPDS.

Based on practicability and the clinimetric properties, it is not possible to choose one of the selected measurement instruments over the other.
Although the ODI and the QBPDS received more votes during the consensus procedure (78% and 62% of the votes respectively), an international multidisciplinary group of experts for scientific research ultimately chose to include the RMDQ (with only 50% of the votes) in the core set, because this measurement instrument is freely available (Chiarotto 2018a).
Out of a group of experts comprised of patients, patient representatives, researchers, physical therapists, policy-makers and health insurance companies, 80% voted to include the QBPDS in the core set and 64% voted to include the ODI (Verburg 2019). They supposed that the ODI is less customary in the Netherlands. The RMDQ was not included in the vote, because it had already been omitted earlier in the consensus process after being discussed within the project group. The project group only presented a limited number of measurement instruments per domain on which to vote. Additionally, alignment with existing guidelines was sought as much as possible.

The guideline panel believes that – keeping in mind the local context and the importance of consistency in the recommendation of measurement instruments – the QBPDS should be included in the guideline for measuring physical functioning as a recommended measurement instrument.

Activities and participation in ADL

The responsiveness of the PSC was assessed in a randomised, controlled study in a subgroup of 81 patients with low back pain for at least 6 weeks. (Beurskens 1996). In this study, the PSC was found to be sufficiently responsive (AUC 0.82), and it could properly discriminate between recovered and non-recovered patients.
No research was done on the validity of the Dutch version of the PSC in patients with low back pain. The questionnaire is sufficiently valid for patients with ankle complaints: 100% of the hypotheses were confirmed in a comparison with the Ankle Function Score and the Molander Ankle Score (Van der Wees 2012). For patients with Parkinson's disease, the reliability is variable and dependent on the selected activity; Cohen's Kappa varies from 0.39 to 0.83 (Nijkrake 2009).
More research was done on the English variant, the Patient-Specific Functional Scale (PSFS).
In a literature review, the PSFS appears to be valid, reliable and responsive in patients with osteoarthritis of the hip or knee (Barten 2012).

Literature for steps 7 and 8 – Are standard values available and how do you calculate and interpret the data?

The calculation method of each instrument was included in the 'practicability' header and is described at www.meetinstrumentenzorg.nl. The calculation of the total score has been included in most electronic patient records.

Interpretation of the total score is about the degree to which importance can be attributed to the (change in) score of the measurement instrument. A measure such as the minimal clinically relevant difference (MCID) or the minimal important change (MIC) can be applied here (KNGF 2016).[1] There are no standard values known for the PSC. The data about the MIC of the other recommended measurement instruments are based on a literature review, an expert panel and a workshop with the goal of developing practical guidelines for oft-used measurement instruments for pain and physical limitations in patients with low back pain (Ostelo 2008). After discussion, consensus was reached in this study about the following MIC values:

> There are some indications that, when taking into account the baseline score, a 30% improvement of the NPRS and/or the QBPDS can be viewed as a useful threshold for identifying a clinically relevant improvement in the individual patient (Ostelo 2008).

Considerations

In accordance with the Framework on Clinimetrics for Evidence-based Products (KNGF 2016), it was first determined which domains or parameters need to be assessed. This is primarily based on items that were found to be important in the medical history taking, the physical examination and the indication assessment. Based on this, recommended and optional measurement instruments were selected. See the substantiations of this module (note B.3) for an overview of the parameters.
The optional measurement instruments can be selected based on clinical reasoning, to support the diagnostic process or for evaluation purposes, if there is a specific reason for this.
For more information about the practicability, clinimetric quality and interpretation of the results of the optional measurement instruments, please refer to www.meetinstrumentenzorg.nl.

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[1] Measures for interpretation (such as the MCID and MIC) are often obtained based on data at the group level. When applying this in practice, the usability may therefore be limited, given that a value that has been obtained at the group level has to be translated to the individual level. Nevertheless, the score on the instrument gives an indication of the individual change in health status. When interpreting the score, floor and ceiling effects must also be taken into account, as these influence the possibility for improvement.

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Note C.1 Information and advice and (pain) education

References

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Note C.2.1 Exercise therapy interventions

Literature

To answer the clinical question, a systematic literature analysis was carried out for the following research question (PICO):

What are the desirable and undesirable effects (O) of exercise therapy (I) versus no exercise therapy or another form of exercise therapy (C) in patients with low back pain with or without sciatica, without important warning signs (P)?
'No exercise therapy' is subdivided into: 1) doing nothing/waiting, 2) placebo/sham, 3) another intervention within the guideline (including information and advice, (pain) education, CGT).

Search

In order to answer the clinical question about exercise therapy, an overview article of systematic reviews about exercise therapy in patients with chronic low back pain was used (Almeida 2020). The studies in this literature review were checked using our pre-established selection criteria. See the following table.

Selection criteria for the search on literature about the effect of exercise therapy on chronic low back pain

Type of studies	Systematic review (possibly as a part of a guideline), published in English or Dutch
Type of patients	Adults with low back pain with or without sciatica, without important warning signs (see A.1 'Introduction') **Exclusion:** Systematic reviews focused on one specific population, such as 'the elderly'
Type of intervention	Exercise therapy, individual or in a group setting, supervised or unsupervised, or exercise therapy as a supplement to information and advice **Exclusion:** Back school, tai-chi, pilates, yoga, swim or walking therapy, Feldenkrais*, invasive interventions (operations, epidural, facet blockade/injections), pelvic floor exercise therapy, exercise therapy as part of a multidisciplinary programme
Type of comparison	Do nothing/wait, placebo/sham, another intervention according to the guideline (including information and advice, (pain) education, cognitive behavioural therapy; CGT), another type of exercise therapy

Type of outcome	At least one of the following outcome measures: **desirable:** • crucial: quality of life, pain, physical functioning • important: work-related outcomes **undesirable:** • all negative effects that might be related to the intervention
Type of timeline	Short (≤4 months) and/or long (>4 months) term; in the event of multiple measurement points, the measurement point that is closest to this time indication applies

* Pilates and Feldenkrais do not fall within the physical therapy domain. Pilates: Exercise therapy according to the original six pilates principles: breathing, concentration, control, precision, center and flow. Feldenkrais: 'By increasing our awareness of our movements, the Feldenkrais Method brings us closer to realising our full human potential' (Dutch Feldenkrais Association).

Additionally, it was assessed whether the systematic reviews that were excluded by Almeida based on 'not chronic' possibly did meet our inclusion criteria. Finally, we updated Almeida's search (the flowchart of this process has been included in appendix C.2.1-1).
Pain and physical functioning were selected for this clinical question as crucial outcome measures for the decision-making process (Chiarotto 2015; ICHOM Working Group Members for Low Back Pain 2017; Verburg 2019). Furthermore, we studied the available literature for a representation of undesirable effects of exercise therapy by assessing all negative effects that may be related to the intervention (e.g. increased pain and/or limitations in physical functioning, or pain and/or limitations in physical functioning of a type other than the kind for which one initially sought help, occurring immediately after the intervention). The results of the identified systematic reviews were analysed and descriptively summarised.
In order to limit an overlap of results between various systematic reviews, the results of the most recent literature reviews with the highest methodological quality according to the AMSTAR-2 score (Shea 2017) were described for each type of exercise therapy. The AMSTAR-2 score established by Almeida was used. For the additional systematic reviews, the AMSTAR-2 score was determined by NS according to Almeida's criteria (see appendix C.2.1-4).
Data about the evidentiary value and the reported estimated effects were extracted from the included systematic reviews. See A.1 'Introduction' for an indication of the clinical relevance of the difference between the intervention and the control group. These values are commensurate with those in the guideline of the National Institute for Health and Care Excellence (De Campos 2017) and the KNGF Guideline on Rheumatoid Arthritis (KNGF 2018).
Almeida included 38 systematic reviews, of which 20 met our selection criteria. Of the 29 systematic reviews excluded by Almeida, two did meet our criteria. Based on the updated search, we included 11 recent systematic reviews (see appendix C.2.1-1 for the flowchart of the updated search). The total number of analysed systematic reviews therefore amounts to 33 (general: n = 15; Motor Control Exercise (MCE): n = 12; MDT: n = 6).

The effectiveness and evidentiary value of exercise therapy

The effectiveness of exercise therapy in general is described in 15 systematic reviews (Chou 2016; Cuenca-Martinez 2018; De Campos 2017; Dvorak 2011; Gordon 2016; Hayden 2005, 2019; Hettinga 2007; Hilde 1998; Kool 2004; Lewis 2005; Liddle 2004; Merepeza 2014; Searle 2015; Slade 2006), of which four are described, after careful selection (Chou 2016; De Campos 2017; Hayden 2005, 2019). The most recent literature review concerns a meta-analysis of individual patient data (Hayden

2019) which was conducted in parallel with an update of a Cochrane review (Hayden 2005). In this review, the effectiveness of exercise therapy was compared to no exercise therapy or other conservative treatment based on individual data from randomised controlled studies with a moderate to low risk of bias in patients with chronic low back pain with or without sciatica (Hayden 2019). The AMSTAR-2 score of this systematic review is 'high' (see appendix C.2.1-5). In addition, two systematic reviews were identified with a 'reasonable' AMSTAR-2 score (Chou 2016; Hayden 2005). The most recent review with a reasonable methodological quality concerns the literature review within the scope of revising the guideline for non-pharmacological therapies for low back pain that was conducted on behalf of the American College of Physicians (APC) and the American Pain Society (APS) (Chou 2016, 2017). For this research, systematic reviews and RCTs up to February 2016 were sought. The results are described based on the literature review within the scope of the previous guideline of the APC/APS (Chou 2007), supplemented by results of a literature review with stricter inclusion criteria (Van Middelkoop 2010) and recent RCTs. The literature review of The Cochrane Collaboration on exercise therapy in patients with non-specific low back pain (Hayden 2005) was also assessed as having 'reasonable methodological quality' according to the AMSTAR-2 score. The study protocols for revising this literature review have been published (Hayden 2012; IJzelenberg 2011). Finally, based on the updated search, a literature review of low methodological quality was identified which was conducted within the scope of a guideline of the National Institute for Health and Care Excellence (NICE) on the non-invasive treatments of low back pain and sciatica (De Campos 2017). The literature review is aimed at patients with low back pain with or without sciatica without the most important warning signs and does not stratify based on chronicity. With this the population is best aligned with the population of our guideline. The meta-analysis of individual patient data is exclusively aimed at chronic low back pain (Hayden 2019), and the studies of reasonable methodological quality stratify the results based on acute, subacute and chronic low back pain (Chou 2016; Hayden 2005). The studies included in the meta-analyses describe a variety of exercise therapies (e.g. strength training, core strengthening, aerobics, Mechanical Diagnosis and Therapy (MDT) according to McKenzie and combined exercise therapy), from individual to group and from personalised exercise therapy to standardised exercise therapy (Hayden 2005, 2019) and strength training, stretching, range-of-motion exercises, motor control exercises (including core stability and Pilates), MDT and the Feldenkrais method (De Campos 2017).
Exercise therapy is compared in the systematic reviews with no exercise therapy including usual care (Chou 2016; Hayden 2005, 2019), or with no exercise therapy and usual care independent of each other (De Campos 2017) and with another conservative treatment (e.g. a combination of information and advice, back classes, manual therapy and psychological therapy (Hayden 2005, 2019) or with self-management, manual therapy or interference (De Campos 2017).

Effectiveness of exercise therapy for acute and subacute low back pain
For exercise therapy compared to no exercise therapy in patients with acute low back pain, very small differences were found in favour of exercise therapy for pain in the short term (MD 0.59 on a scale of 0 to 100; 95% CI -11.51 to 12.69; 3 RCTs, 491 participants) and physical functioning in the short term (MD -2.82 on a scale of 0 to 100; 95% CI -15.35 to 9.71; 3 RCTs) (Chou 2016; Hayden 2005). Comparable results were seen for the medium term and long term (Hayden 2005). The evidentiary value for pain and physical functioning in patients with acute low back pain is low (Chou 2016). There was also a small difference for pain in the short term compared to other conservative treatments in favour of exercise therapy (MD -0.31 on a scale of 0 to 100; 95% CI: -0.72 to 0.10; 7 RCTs, 606 participants) (Hayden 2005).

For subacute low back pain there were also small differences between exercise therapy and no exercise therapy regarding pain in the short term (Hayden 2005 reports an MD of −8.0 on a scale of 0 to 100; 95% CI −17.25 to 1.25; 1 RCT, 194 participants and Chou 2016 reports an MD of 1.89 on a scale of 0 to 100; 95% CI −1.13 to 4.91; 5 studies) and physical functioning in the short term (Chou 2016 reports an MD of 1.07 on a scale of 0 to 100; 95% CI −3.18 to 5.32; 4 studies). The evidentiary value of exercise therapy in relation to pain and physical functioning in patients with subacute low back pain is low (Chou 2016). There was also a very small difference between the effect of exercise therapy on pain in the short term compared to other conservative treatments (MD of −1.21 on a scale of 0 to 100; 95% CI: −4.01 to 1.59; 4 RCTs, 414 participants) (Hayden 2005). This also applied to physical functioning in the short term for patients with subacute low back pain (Hayden 2005). The results are comparable for the medium term and long term (Hayden 2005). Given that the Cochrane review by Hayden from 2012 was published before the GRADE methodology was implemented, no assessment was made of the evidentiary value per outcome measure. Based on the risk of bias (RoB), it was concluded that the quality of the included studies is low as a result of the heterogeneity of the outcome measures, inconsistency and possible publication bias.

Effectiveness of exercise therapy for chronic low back pain

Based on a meta-analysis with individual patient data in patients with chronic low back pain with or without sciatica, it was determined that there is a clinically relevant difference between the effects of exercise therapy and no treatment or usual care on pain in the short term (MD −10.7 on a scale of 0 to 100; 95% CI −14.1 to −7.4; 26 studies, 2,466 participants) in favour of exercise therapy (Hayden 2019). The results of the effects of exercise therapy compared to no exercise therapy on pain in the short term from the literature review of Chou are aligned with the results of the study by Hayden from 2019; exercise therapy is associated with more pain alleviation compared to no exercise therapy (MD 10 on a scale of 0 to 100; 95% CI 1.31 to 19.09; 19 studies) (Chou 2016). The studies on the effects of exercise therapy compared to no treatment or usual care on pain in the short term have shown consistent results for a decade already: for patients with chronic low back pain, the meta-analysis of Hayden from 2012 shows a positive effect of exercise therapy, with a comparable estimated effect, on pain in the short term (MD −10.20 on a scale of 0 to 100; 95% CI −19.09 to −1.31; 8 RCTs, 370 participants). Fewer data are available on the effectiveness of exercise therapy compared to no exercise therapy in the long term. There was a small difference found in favour of exercise therapy compared to no treatment/sham/placebo for pain in the long term (MD −3.93 on a scale of 0 to 100; 95% CI: −9.89 to 2.02; 5 RCTs, 126 participants). The estimated effects of exercise therapy compared to no treatment on physical functioning in the short term vary from a reasonable amount in the most recent meta-analysis (MD −10.2 on a scale of 0 to 100; 95% CI −13.1 to −7.3; 25 studies, 2,366 participants) of Hayden from 2019 (Hayden 2019) to a small amount (MD 3.00 on a scale of 0 to 100; 95% CI −0.53 to 6.48; 17 studies) in the Conchrane review of Hayden from 2005 (Hayden 2005). This last study shows that the long-term results are comparable (Hayden 2005). Neither the study from 2005 nor the one from 2019 states anything about the evidentiary value according to GRADE. The meta-analysis from 2019 only includes RCTs with a low risk of bias. There is, however, large heterogeneity; the point estimates and confidence intervals vary significantly (I2 91%; p <0.00001), which with a GRADE assessment would result in a down-grading of the evidentiary value due to inconsistency. Given the large sample and the not very large confidence interval, there does not appear to be a reason to down-grade for imprecision. There is also no reason to down-grade for indirectness. The assessment of the evidentiary value should come out to reasonable, which correlates with the assessment of the evidentiary value in other literature reviews (Chou 2016).

For the effectiveness of exercise therapy compared to other conservative treatment, conflicting results were found for pain and physical functioning in the short term. The literature review of Hayden from 2005 shows a small difference in favour of exercise therapy (MD for pain −5.93 on a scale of 0 to 100; 95% CI −9.65 to −2.21; 15 RCTs, 1,327 participants and MD for physical functioning −2.37 on a scale of 0 to 100; 95% CI −2.00 to −0.74; 13 RCTs, 1,373 participants), while the literature review of Hayden from 2019 shows a small difference in favour of the other conservative treatments (MD for pain 3.7 on a scale of 0 to 100; 95% CI 1.3 to 6.0; 26 RCTs, 2,850 participants and MD for physical functioning 1.9 on a scale of 0 to 100; 95% CI 0.03 to 3.8; 25 RCTs, 2778 participants).
A small difference was found in favour of exercise therapy compared to other conservative treatment for pain in the long term (MD −7.62 on a scale of 0 to 100; 95% CI −14.45 to −0.79; 9 RCTs; 906 participants) and for physical functioning in the long term (MD −4.34 on a scale of 0 to 100; 95% CI −6.00 to −0.69; 9 RCTs; 1,026 participants).

Effectiveness of exercise therapy for acute, subacute and chronic low back pain (no stratification based on chronicity)
The literature review that was conducted within the scope of the NICE guideline is aimed at patients with low back pain with or without sciatica without the most important warning signs and does not stratify based on chronicity (De Campos 2017). The literature review mentions biomechanical exercise therapy, which entails muscle strengthening, stretching, exercises to improve motor control and other forms of exercise therapy, such as MDT and Feldenkrais.
A small difference was found in favour of individual biomechanical exercise therapy compared to usual care for pain in the short term (MD 0.74 on a scale of 0 to 10; 95% CI −1.12 to −0.36; 5 studies; 317 participants; moderate evidentiary value) and a very small difference for pain in the long term (MD 0.08 on a scale of 0 to 10; 95% CI −1.53 to 1.37; 1 RCT, 99 participants, low evidentiary value) (De Campos 2017). No clinical benefit was found of individual biomechanical exercise therapy compared to usual care for physical functioning in the short term (average score in the control group was 17.74 on the scale of 100, average score in the intervention group was 1.31 SDs lower; 95% CI −2.75 to −0.15; 5 RCTs, 253 participants, low evidentiary value) or long term (average score in the control group was 18.78 on the scale of 100, average score in the intervention group was 0.32 SDs lower; 95% CI −0.66 to 0.01; 2 RCTs, 159 participants; low evidentiary value) (De Campos 2017).
Regarding individual biomechanical exercise therapy compared to other conservative treatment, the literature review states the following: *"Evidence was found of the clinical benefit of individual biomechanical exercises compared to self-management, manipulation of the spine and interference therapy, usually from small individual studies of low or very low quality. The evidence only showed a clinical benefit for biomechanical exercise therapy for pain in the legs in the long term (1 study; low quality; n = 71) and physical functioning in the long term (1 study; very low quality; n = 71) compared to self-management"* (De Campos 2017). (vert. redactie)

The effectiveness and evidentiary value of motor control exercise (MCE)
The effectiveness of MCE is described in 12 systematic reviews (Brumitt 2013; Bystrom 2013; Chang 2015; Elbayomy 2018; Gomes-Neto 2017; Luomajoki 2018; Macedo 2016; Niederer 2020; Rackwitz 2006; Saragiotto 2016; Slade 2006; Wang 2012), of which two were selected within the scope of this description (Macedo 2016; Saragiotto 2016). No systematic reviews were found about MCE in patients with low back pain of high or reasonable methodological quality according to the AMSTAR-2 score. The methodological quality of the four selected systematic reviews was

assessed as low. In 2016, two literature reviews were published by The Cochrane Collaboration on the effectiveness of exercise therapy for patients with acute (Macedo 2016) and chronic (Saragiotto 2016) non-specific low back pain.
MCE applies principles of motor learning in order to integrate control and coordination of the spinal muscles during functional activities. This also includes specific stabilisation training of the spine, for example through strength or coordination training of the multifidus muscle and the transverse abdominal muscle (Macedo 2016; Saragiotto 2016).

Effectiveness and evidentiary value of MCE for acute and subacute low back pain
Only three small RCTs were identified about the effectiveness of MCE for acute low back pain with or without sciatica, which evaluated different comparisons (Macedo 2016). No RCTs were found that compared MCE with no treatment.
Compared to other forms of exercise therapy, a small difference was found in the effectiveness of MCE for pain in the short term (MD 5.74 on a scale of 0 to 100; 95% CI −3.34 to 14.82; 2 RCTs, 89 participants, moderate evidentiary value) and in the medium term (MD −1.20 on a scale of 0 to 100; 95% CI −18.24 to 15.84; 1 RCT, 33 participants, low evidentiary value). There were also small differences found for physical functioning in the short term (MD −0.84 on a scale of 0 to 100; 95% CI −8.72 to 7.04; 2 RCTs, 116 participants, moderate evidentiary value), in the medium term (MD −6.70 on a scale of 0 to 100; 95% CI −22.80 to 9.40; 1 RCT; 33 participants, low evidentiary value) and in the long term (MD 5.70 on a scale of 0 to 100; 95% CI −1.38 to 12.78; 1 RCT, 83 participants, low evidentiary value).
For acute low back pain, compared to manipulation a small difference was found in the effectiveness of MCE for pain in the short term (MD 9.00 on a scale of 0 to 100; 95% CI −1.56 to 19.56; 1 RCT, 58 participants) and for physical functioning (MD 4.00 on a scale of 0 to 100; 95% CI −3.38 to 11.38; 1 RCT, 95 participants). This small difference was also observed for physical functioning in the long term (MD 3.70 on a scale of 0 to 100; 95% CI: −4.10 to 11.50; 1 RCT, 95 participants). The evidentiary value was low for all cases.
MCE in combination with medical management (advice to take bed rest, not work and resume daily activities, if possible, in combination with pain medication) results in small effects on pain in the short term (MD −9.30 on a scale of 0 to 100; 95% CI −20.41 to 1.81; 1 RCT, 42 participants) and physical functioning (MD −0.90 on a scale of 0 to 100; 95% CI −4.77 to 2.97; 1 RCT, 41 participants). However, the evidentiary value is very low.

Effectiveness and evidentiary value of MCE for chronic low back pain
One systematic review reported on the effectiveness of MCE in patients with chronic low back pain (Saragiotto 2016). Compared to minimal intervention (placebo physical therapy, education or advice and no treatment), a clinically relevant difference was found for pain in favour of MCE in the short term (MD −10.01 on a scale of 0 to 100; 95% CI −15.67 to −4.35; 4 RCTs, 291 participants, moderate evidentiary value), in the medium term (MD −12.61 on a scale of 0 to 100; 95% CI −20.53 to −4.69; 4 RCTs; 348 participants, low evidentiary value) and in the long term (MD −12.97 on a scale of 0 to 100; 95% CI −18.51 to −7.42; 3 RCTs, 279 participants, moderate evidentiary value) (Saragiotto 2016). This also applies to physical functioning: in the short term (MD −8.63 on a scale of 0 to 100; 95% CI −14.78 to −2.47; 5 RCTs, 332 participants, low evidentiary value), in the medium term (MD −5.47 on a scale of 0 to 100; 95% CI −9.17 to −1.77; 4 RCTs; 348 participants, moderate evidentiary value) and in the long term (MD −5.96 on a scale of 0 to 100; 95% CI −9.81 to −2.11; 3 RCTs, 279 participants, moderate evidentiary value) (Saragiotto 2016).

Compared to other forms of exercise therapy, there is also a small difference in favour of MCE for pain both in the short term (MD −7.53 on a scale of 0 to 100; 95% CI −10.54 to −4.52; 13 RCTs, 872 participants, low evidentiary value), in the medium term (MD −2.98 on a scale of 0 to 100; 95% CI −6.96 to 0.99; 6 RCTs; 588 participants, high evidentiary value) and in the long term (MD −2.69 on a scale of 0 to 100; 95% CI −6.90 to 1.53; 5 RCTs, 643 participants, high evidentiary value). This also applies to the physical functioning outcome measure: in the short term (MD −4.82 on a scale of 0 to 100; 95% CI −6.95 to −2.68; 11 RCTs, 794 participants, low evidentiary value), in the medium term (MD −2.88 on a scale of 0 to 100; 95% CI −6.92 to 1.15; 10 RCTs; 588 participants, high evidentiary value) and in the long term (MD −0.71 on a scale of 0 to 100; 95% CI −4.87 to 3.45; 4 RCTs, 570 participants, high evidentiary value) (Saragiotto 2016).
Compared to manual therapy, there is a small difference in favour of MCE for pain in the short term (MD −4.36 on a scale of 0 to 100; 95% CI −9.52 to 0.81; 3 RCTs, 282 participants, moderate evidentiary value), in the medium term (MD −7.05 on a scale of 0 to 100; 95% CI −14.20 to 0.11; 4 RCTs; 485 participants, moderate evidentiary value) and in the long term (MD −3.67 on a scale of 0 to 100; 95% CI −9.28 to 1.94; 4 RCTs, 406 participants, high evidentiary value). This also applies to the physical functioning outcome measure: in the short term (MD −2.79 on a scale of 0 to 100; 95% CI −6.60 to 1.02; 3 RCTs, 282 participants, moderate evidentiary value), in the medium term (MD −3.28 on a scale of 0 to 100; 95% CI −6.97 to 0.40; 4 RCTs; 485 participants, high evidentiary value) and in the long term (MD −3.40 on a scale of 0 to 100; 95% CI −7.87 to 1.07; 4 RCTs, 406 participants, high evidentiary value) (Saragiotto 2016).
The adverse effects of MCE are minimal, if reported (Saragiotto 2016).

The effectiveness and evidentiary value of Mechanical Diagnosis and Therapy (MDT) according to McKenzie

Effectiveness of MDT for acute and subacute low back pain

The effectiveness of MDT is described in six systematic reviews (Alhakami 2019; Czajka 2018; Dunsford 2011; Lam 2018; Machado 2006; Namnaqani 2019), which are all of very low methodological quality (see appendix C.2-5). Based on the topicality and alignment with the clinical question, the results of two systematic reviews are described in more detail in this guideline (Lam 2018; Machado 2006). The literature review of the Cochrane Collaboration on MDT for non-specific low back pain (Machado 2006) is currently being revised (Machado 2012a, b).
The results of the currently valid Cochrane review show a small positive difference of MDT on pain in patients with acute low back pain (MD −4.16 on a scale of 0 to 100; 95% CI −7.12 to −1.20; 2 RCTs; 375 participants) as well as on physical functioning (MD −5.22 on a scale of 0 to 100; 95% CI −8.28 to −2.16; 2 RCTs; 375 participants) in the short term compared to passive therapy (information folders, bed rest, cooling and massage) for patients with acute low back pain (Machado 2006).
When MDT is compared to the advice to remain active, a benefit is found in favour of the advice to remain active for pain (MD 5.02 on a scale of 0 to 100; 95% CI −1.19 to 11.22; 2 RCTs, 178 participants) and for physical functioning (MD 3.85 on a scale of 0 to 100; 95% CI 0.30 to 7.39; 2 RCTs, 178 participants) in the short term (Machado 2006).
The results of the Cochrane review are limited to patients with acute low back pain. As a result of heterogeneity, the results for patients with chronic low back pain have not been pooled. No RCTs were found that made a comparison with waiting/doing nothing/placebo/sham (Machado 2006).
Given that the Cochrane review was published before the GRADE methodology was implemented, no assessment was made of the evidentiary value per outcome measure. Based on the risk-of-bias

assessment and the results, our estimation is that the evidentiary value will at least be down-graded as a result of limitations in the study design and execution, and imprecision, resulting in low evidentiary value.
Arguing against the results is the fact that a generic application of MDT was investigated in many studies, without taking the classification of patients into account. For this reason, the objective of the systematic review by Lam was to determine whether there was a difference between the effectiveness of MDT on pain and physical functioning when this was administered by trained therapists, and the effectiveness of various other types of interventions in patients with acute and chronic low back pain. This is why Lam only included studies with therapists who had received MDT training (Lam 2018).
The results show that exercise therapy according to MDT for patients with acute low back pain leads to a clinically relevant difference for pain in the short term (SMD −0.45; 95% CI −0.99 to 0.10; 3 RCTs, 194 participants) compared to another intervention (manual therapy and primary care treatment consisting of information and advice and pain medication), with moderate evidentiary value. There was also a very small positive difference with MDT in patients with acute low back pain for physical functioning in the short term (SMD −0.07; 95% CI −0.34 to 0.20; 4 RCTs, 457 participants), with high evidentiary value (Lam 2018).

Effectiveness and evidentiary value of MDT for chronic low back pain
For patients with chronic low back pain, MDT leads to a clinically relevant positive difference for pain in the short term (SMD −0.33; 95% CI −0.63 to −0.03; 6 RCTs, 714 participants) compared to another intervention (manual therapy in combination with exercise therapy), with moderate evidentiary value. Finally, exercise therapy according to MDT results in a small difference for physical functioning in the short term (SMD −0.28; 95% CI −0.44 to −0.12; 7 RCTs, 859 participants) compared to another intervention (manual therapy in combination with exercise therapy), with high evidentiary value (Lam 2018). The evidentiary value in the systematic review of Lam was assessed as moderate and high according to GRADE. However, when assessing the evidentiary value, no down-grading took place for risk of bias and imprecision, even though there was a reason to do so (a cut-off value of 5/10 on the PEDro score is used as a criterion for down-grading for risk of bias, with low numbers of patients and with broad confidence intervals). The long-term results of MDT are largely unknown.

Considerations
There are a large number of international guidelines for patients with low back pain. Exercise therapy is recommended in 10 of the 14 guidelines for patients with chronic non-specific low back pain in a primary care setting (Oliveira 2018). However, the methodological quality of the guidelines often leaves a lot to be desired (Lin 2018). Exercise therapy is recommended in all cases in the guidelines of high methodological quality (Almeida 2018; Lin 2019; Malfliet 2019), specifically:

- the guideline of the National Institute for Health and Care Excellence (NICE) (De Campos 2017);
- the guideline of the Belgian Health Care Knowledge Centre (KCE) (Van Wambeke 2017);
- the guideline of the Danish Health Authority (Stochkendahl 2018);
- the guideline of the American College of Physicians (Qaseem 2017b);
- the Canadian guideline of the OPTIMa alliance (Wong 2017);
- the Canadian Chiropractic Guideline (Globe 2016).

To answer the clinical question, other considerations were also included in the literature to recommendation process in addition to the literature. Together they determine the direction and strength of the recommendation. The assessment of considerations and the explanation are provided in appendix C.2.1-3.

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Note C.2.2 Type, frequency, intensity and time span of exercise therapy

Literature

There are a large number of (inter)national guidelines about low back pain These guidelines are described in a number of overview articles, including an assessment of methodological quality (Almeida 2018; Krenn 2020; Lin 2019; Malfliet 2019). The recommendations of guidelines of high methodological quality about frequency, intensity, type and time span of the exercise therapy are provided below.

The guideline of the National Institute for Health and Care Excellence (NICE) (De Campos 2017) recommends exercise therapy in general. The proof between specific types of exercise therapy varied, but the authors of this guideline did not find the evidence to be sufficient in order to formulate a recommendation for the optimal type, the optimal dose or the optimal duration of the exercise therapy. The NICE guideline states that it is important to set up the intervention so that it is likely that the patient with back pain will participate in it and that the intervention encourages self-management. It is deemed important for the exercise therapy to be aligned with the patient, while also taking into account a feasible dosage, so that the patient can keep up the exercise therapy. The guideline of the Belgian Health Care Knowledge Centre (KCE) (Van Wambeke 2017) also recommends exercise therapy, but no specific recommendation is given about its dosage. The recommendation is to let the patient's needs, capacities and preferences be decisive for the type of exercise therapy. The guidelines of the Danish Health Authority (Stochkendahl 2018) and the Canadian Chiropractic Guideline (Globe 2016) do not make any statements about the type and dosage of the exercise therapy (Globe 2016; Stochkendahl 2018). Finally, the guideline of the American College of Physicians (Qaseem 2017) recommends exercise therapy in general and motor control exercises, but this guideline also does not state anything about the dosage thereof. The guideline of the North American Spine Society (NASS) 2020 conducted a systematic review on the optimal timing, frequency and time span of the exercise therapy, but this did not yield any studies with which this question could be adequately answered.

The guideline of the American College of Sports Medicine (ACSM) for exercise therapy

The current (10th) edition of the ACSM Guidelines for Exercise Testing and Prescription describes four components that are important for prescribing exercise therapy: Frequency, Intensity, Type and Time Span (FITT) (American College of Sports Medicine 2017). The recommendations of the guideline panel on exercise therapy for patients with low back pain per type of exercise therapy are based on this guideline (American College of Sports Medicine 2017, 2018). Scientific research in the past 40 years has demonstrated that physical activity and exercise therapy in combination with other lifestyle-related topics play an important role in the prevention, treatment and rehabilitation of various conditions.

Various domains of health can be defined: emotional health, social health, physical health, mental health and spiritual health. Physical activity and exercise therapy concern the physical domain, but interactions between the various components of the domains are unmistakable. Exercise therapy is only one element that contributes to a person's overall health. Other domains are also important for determining a treatment plan (American College of Sports Medicine 2018). The basis for setting up a good exercise therapy programme is shaped by the knowledge that the professional has of the indications and the contraindications for exercise therapy in a specific population and the correct use of the FITT principles.
The guidelines for the FITT principles for patients with low back pain are similar to the guidelines for healthy people (American College of Sports Medicine 2018). Training responses are typically influenced by the severity and location of the pain, physical fitness and strength, and body positions that are required during exertion. Some people with low back pain do not tolerate certain movements, such as trunk flexion or extension. Additionally, some body positions, such as standing or sitting for a long time, may cause discomfort, thereby preventing the patient from training in an optimal manner.
The ACSM's recommendations for the FITT principles for patients with low back pain are as follows (American College of Sports Medicine 2018):

- Frequency (how often?): ≥ 5 d * wk^{-1} moderate exertion or ≥ 3 d * wk^{-1} heavy exertion or a combination of moderate and heavy exertion ≥ 3 to 5 d * wk^{-1}.
- Intensity (how intensively?): moderate to heavy exertion.
- Time: ≥ 30 min d * wk^{-1} of consecutive exercise for at least 10 minutes.
- Type (primary): exercise therapy for improving the aerobic endurance in body positions that are tolerated the best.
- Strength training: 2 to 3 d * wk^{-1} (not consecutive); 2 to 4 sets of 8 to 12 repetitions at 60 to 70% of 1RM for most adults; 10 to 15 repetitions at 40 to 50% of 1RM for people who do not have experience with strength training and the elderly.
- Flexibility: 2 to 3 d * wk^{-1}; exercise until you feel stretched or slight discomfort during 10 to 30 seconds for most adults and 30 to 60 seconds for the elderly; 2 to 4 repetitions of each stretch exercise, within the patient's capabilities.
- Specific considerations: an individualised exercise programme aimed at all health-related fitness variables, comorbidity (if present) and preferred body positions can improve the compliance with the programme, the effectiveness and the health-related quality of life and contribute to a more physically active lifestyle.

The other considerations for exercise therapy for patients with low back pain are summarised in the ACSM guideline as follows (American College of Sports Medicine 2018):

- the exercise programme must be individualised, and the objectives must be aimed at all health and fitness needs of people with low back pain;
- there may be comorbidity that helps shape the exercise programme;
- if present, preferred body positions or limited range of motion can determine the positions in which strength and flexibility training is performed;
- exercises that cause pain during or after training sessions must be eliminated and replaced by alternative activities;

- new or worsening symptoms justify ending the training and communication with a physician and/or healthcare provider (for implementation of this recommendation, see C.5 'Completion of the treatment' in the current guideline);
- exercises or activities with a major impact (e.g. running) must be avoided or built up gradually with the appropriate care;
- persons with low back pain must learn fundamental movement patterns, such as squatting and lifting something from the ground, and must avoid sitting for long periods.

Neuromotor exercise therapy is not considered in the ACSM guideline's recommendations for the FITT principles for patients with low back pain. Neuromotor exercise therapy is a component of the FITT principles for healthy participants (American College of Sports Medicine 2017), even though the guideline states that the effectiveness of this exercise therapy in adults has not yet been proven (Garber 2011). The ACSM guideline specifies neuromotor training of healthy participants (American College of Sports Medicine 2017): *"Neuromotor training involving balance, agility, coordination and gait analysis is recommended for at least two to three days per week for healthy older people and is likely also beneficial for adults in general"*.
The optimal duration or the optimal number of repetitions of neuromotor training is still largely unknown, but neuromotor exercises of at least 20 to 30 minutes and in total 60 minutes per week may be effective (Garber 2011). Neuromotor training is also known in the international literature as functional training and may overlap with other established types of exercise, such as strength training.

Considerations

Type of exercise therapy

Exercise therapy is recommended for patients with low back pain (see C.2.1 'Exercise therapy interventions'). Research has demonstrated that, among other things, a general exercise programme for improving muscle strength, flexibility and aerobic endurance has a favourable effect on recovery of low back pain (Gordon 2016) and that training for improved aerobic endurance can decrease the pain intensity and improve the physical and psychological functioning of patients with chronic low back pain (Meng 2015). However, there is not a certain type of exercise therapy that is consistently recommended within the international guidelines (Almeida 2018; Lin 2019; Malfliet 2019; Oliveira 2018). The current literature also does not provide a definitive answer as to which type of exercise therapy is indicated for which patient. The guideline panel therefore finds it important to focus the exercise therapy on the patient's needs, preferences and capabilities as determined during the medical history taking and the physical examination. The guideline panel also believes it's important for the therapist to assess, based on clinical expertise, whether the dysfunctions that are ascertained during the diagnostic process are related to the complaints and for the choice of exercise therapy (muscle strength, aerobic endurance, flexibility or a combination thereof) to be based on a logical construct.

Exercise therapy for improving muscle strength, aerobic endurance and flexibility

In daily practice, the treatable traits for treating the individual patient are assessed during the medical history taking and the physical examination. The important aspects have been specified based on the ICF 'core set' for people with low back pain (Cieza 2004) (see B.1.1 'Medical history taking' and B.1.2 'Physical examination'). The identified health problems concern dysfunctions

with respect to muscle strength, joint mobility, exercise tolerance, muscle endurance, muscle tone and stability of joints. Cross-sectional research, for example, has shown that in persons with chronic low back pain, the muscle strength of the hip abductors (Arab 2010; Cooper 2016; De Sousa 2019; Kendall 2010), lumbar extensors (Kankaanpaa 1998) and flexors of the lumbar spine is often reduced compared to that of healthy participants. Decreased length of the hamstrings has also been associated with low back pain in the scientific literature (Hori 2019; Sadler 2017). Exercise therapy is therefore often aimed at improving these parameters.

Exercise therapy for improving neuromotor control

Cross-sectional laboratory studies have shown that people with low back pain have decreased control of their deep trunk muscles (e.g. the transverse abdominal muscle and the multifidus muscle), which are partially responsible for maintaining stability of the spine (Hodges 1996). There are also indications that patients with low back pain move the lumbopelvic region earlier during functional movements and with a larger range of motion than people without low back pain (Marich 2017; Scholtes 2009; Sorensen 2016). This may also be a manifestation of decreased stability of the low back. In addition to the established types of exercise therefore, exercise therapy for improving neuromotor control is also often used. In the ACSM guidelines, neuromotor exercise therapy includes balance, coordination and proprioception training. There has been increasing attention given to MCE in recent scientific literature about low back pain (Macedo 2016; Saragiotto 2016). MCE can be viewed as a type of neuromotor exercise therapy. This type of exercise applies principles of motor learning in order to integrate control and coordination of the spinal muscles in functional activities. This also includes specific stabilisation training of the spine, for example through strength or coordination training of the multifidus muscle and the transverse abdominal muscle. C.2.1 'Exercise therapy interventions' discusses the effectiveness of MCE in more detail. The guideline panel believes that neuromotor exercise therapy can be considered if there is disrupted neuromotor control, balance and/or stability of the lumbar spine and if the therapist assesses that there is a connection between this disruption and the complaints. The guideline panel recognises the ACSM's finding regarding the lack of scientific substantiation of the optimal duration or the optimal number of repetitions of the neuromotor training. The guideline panel does not agree with the frequency (at least 2-3 days per week) and time span (at least 20-30 minutes and a total of 60 minutes per week) that the ACSM describes. Instead of a fixed exercise regimen, the guideline panel believes it is more important to coordinate the implementation and expansion of the programme to the patient's capacity, with the accent being on the quality of movement without increased pain. This is in line with the developments in the scientific literature, where better short-term and long-term effects were seen for physical functioning in people who received this type of training than with regular training (Van Dillen 2020).

Functional training

A specific recommendation has been included in the ACSM guidelines for exercise therapy for patients with low back pain (American College of Sports Medicine 2018) about learning the fundamental movement patterns, such as squatting to lift something from the ground and avoiding sitting for long periods of time. With the advice on avoiding sitting for long periods of time, the guideline panel is in line with the Dutch Physical Activity Guidelines.

The Dutch Physical Activity Guidelines (Dutch Health Council 2017)

- Exercise is good; more exercise is better.
- Do at least 150 minutes per week of moderately intensive exercise, such as walking and biking, spread out over several days. Longer, more frequent and/or more intensive exercise has an additional health benefit.
- Perform muscle and bone strengthening activities at least twice per week, combined with balance exercises in the case of elderly patients.
- Avoid sitting still too much.

The guideline panel believes that learning fundamental movement patterns is only indicated if the patient has a dysfunction in this, such a dysfunction is ascertained by the therapist and/or the need for assistance is aimed at this dysfunction. The guideline panel does, however, believe it is important to integrate functional training, specifically (parts of) activities in which the patient is limited, into the exercise therapy, among other things for reason of therapy compliance.

The influence of comorbidity on exercise therapy

See A.2.1 'Epidemiology, pathophysiology and comorbidity' for frequent comorbidity with low back pain. The guideline panel recognises the ACSM's finding that there may be comorbidity that helps shape the exercise programmes (American College of Sports Medicine 2018). The guideline panel believes that the exercise therapy must be modified if the comorbidity impedes physical functioning.

Frequency and intensity of the exercise therapy

In systematic reviews about exercise therapy in adults with chronic pain, the most common frequency is at least twice per week and the most common duration of a session is 45 to 60 minutes (Geneen 2017), without differentiating between the various types of exercise therapy. The intensity of the sessions is not quantified in most cases (Geneen 2017), and if it has been quantified, the rationale behind this choice is not explained (Gallois 2017). Recent systematic review emphasises the necessity of doing more research on the dosage of exercise therapy for various subgroups of patients with low back pain (Ojha 2020).

The guideline panel believes that when performing the exercise therapy, the frequency, intensity and time span as stipulated by the ACSM should be strived for. The guideline panel also believes it is important to keep in mind what is feasible for the patient when selecting the dosage of the exercise therapy. For purposes of therapy compliance, it is important for the patient to be able to keep up the exercise therapy.

The ACSM guidelines for scaling up exercise therapy in healthy participants recommend gradually making the exercise therapy more difficult in order to improve aerobic endurance by increasing the duration, frequency or intensity of the exercise programme, or all three (American College of Sports Medicine 2018 American College of Sports Medicine 2017). The degree to which the exercise therapy is made more difficult depends on the patient's health status and physical fitness, the patient's response to the training and the training programme's objectives. The guideline panel agrees with the ACSM guideline.

In the beginning phase of the training programme, it is wise to adopt the start low and go slow principle in order to decrease the risks of cardiovascular events and musculoskeletal injury and to encourage acceptance and therapy compliance. The recommendation is to start with light to

moderate intensity for inactive persons and then increase the training time and duration within the patient's tolerance level (American College of Sports Medicine 2018).
The guideline panel also believes it is important to adhere to a modified version of the 24-hour rule (Egmond 2019) and to inform the patient about the desirable and undesirable training responses. After an exercise or training session, an acceptable (desirable) response is:

- no response, or
- a response (tolerable pain, fatigue or functional problems) that lasts a maximum of 24 hours and then subsides.

An undesirable response is:

- if (night-time) pain, fatigue and loss of function increase after 24 hours.

Duration of the exercise therapy

The ACSM guideline does not contain specific information about the desired duration of the exercise therapy intervention. The ACSM guideline does describe the recommended quality and quantity of the implementation, with the ultimate goal of achieving and retaining these. With regard to the recommendations for scaling up the exercise therapy, four to six weeks are assumed for the average healthy test subject, and four to eight months for older or severely deconditioned persons (American College of Sports Medicine 2017, 2018).
Systematic review describes a duration of four to six weeks for the examined neuromotor exercise therapy interventions for patients with acute low back pain (Macedo 2016) and a duration of 20 days to 12 weeks for patients with chronic low back pain (Saragiotto 2016). However, the included RCTs often adopt a one-size-fits-all approach with a defined course, with the patient's need for assistance playing no (or only a subordinate) role. A recent article in which a tool is developed for evaluating the quality of exercise therapy programmes that were applied in RCTs emphasises the importance of targeted exercise therapy, among other things, whereby a discrepancy between the complaints or limitations of the patient population and the objective of the exercise therapy can result in suboptimal effects (Hoogeboom 2020). In a series of articles about evidence-based management of chronic low back pain, at least 10 to 12 weeks of strength training is assumed in order to achieve a physiological adjustment in the musculature. (Mayer 2008). Functional benefits in the early stages (0 to 6 weeks) of muscle strength training are primarily the result of neurological adaptations such as inter- and intramuscular coordination. In the later stages (6 to 12 weeks) of muscle strength training, the functional benefits are the result of physiological changes, and after 12 weeks there is hypertrophy. The guideline panel ascertains that in daily practice the patient's need for assistance and the treatment goals are guiding when determining the duration of the exercise therapy. A physiological adjustment is not always necessary to reach the treatment goals and answer the patient's need for assistance. What's more, it's not always known whether the physiological adjustment is related to a decrease of complaints. Regarding exercise therapy for improving aerobic endurance, the guideline panel believes it is important to at least strive for a level that is in line with the Dutch Physical Activity Guidelines (Dutch Health Council 2017). These general recommendations are the basis that each individual should comply with. If it is determined during the diagnostic process that the patient with low back pain does not comply with the Dutch Physical Activity Guidelines, information and advice is given about this, in order to encourage overall physical activity (see C.1 'Information and advice and (pain) education').

The guideline panel concludes that the duration of the exercise therapy will differ from patient to patient and finds it important to determine this duration prior to the start of treatment based on consultation between the therapist and patient. This will promote therapy compliance and prevent unnecessary continued treatment. Here one can take into account the severity and duration of the complaints, comorbidity, the presence of (psychosocial) prognostic factors and the possibility of self-management on the part of the patient. The treatment is evaluated every three weeks based on the need for assistance and the treatment goals and is modified or ended, if applicable (see 'C.5 Completion of the treatment').
The guideline panel also believes it is important for the therapist to encourage the patient to continue exercising and moving independently also after the treatment period. The therapist can schedule one or more follow-up sessions for this, for example. The goal of these sessions is to promote therapy compliance, and they can be scheduled at the moment that the scope of the supervised exercise therapy is reduced and independent exercising and physical activity predominate.

Supervised exercise therapy

The selected literature does not provide a definitive answer about supervision of exercise therapy. The guideline panel believes that exercise therapy can be indicated if there is dysfunction in muscle strength, aerobic endurance, flexibility or neuromotor control, whereby there appears to be a correlation with the onset or persistence of complaints. If a patient is not able to independently perform the exercise therapy, temporary supervision by a physical therapist or exercise therapist can offer a solution. The supervision is scaled back during the treatment period, if permissible and in consultation with the patient. Here it is important for the exercise frequency and intensity not to decrease but rather for the focus to shift to independent exercising and physical activity.

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Note C.3 Behaviour-oriented treatment

Literature

To answer the clinical question, the following research question was formulated:

- Are behaviour-oriented treatments administered by a physical therapist or exercise therapist, possibly in addition to active treatment, recommended for patients with low back pain with or without sciatica for pain alleviation and improved physical functioning and quality of life?

Behaviour-oriented treatments are understood to mean operant conditioning (e.g. graded activity), cognitive behavioural therapy (e.g. exposure exercises) and respondent techniques (e.g. relaxation exercises). In this guideline, techniques stemming from or associated with behavioural therapy are also covered by behavioural therapy treatment. For example, techniques that utilise the relationship between cognitions, emotions and behaviour whose goal is to change how a patient copes with pain, such as Acceptance and Commitment Therapy (ACT), interview techniques (e.g. motivational interviewing) and types of pain education. Pain education is described in C.1 'Information and advice and (pain) education'.

To elaborate on this clinical question, in consultation with the guideline panel and the review panel, evidence-based guidelines of high methodological quality were used that comment on behaviour-oriented and/or cognitive behavioural approaches, specifically:

- the British (multidisciplinary) Guideline on Low Back Pain and Sciatica in Over 16s: Assessment and Management, published by the National Institute for Health and Care Excellence (NICE) (De Campos 2017);
- the guideline of the Belgian Health Care Knowledge Centre (KCE) (Van Wambeke 2019), published in Flemish, French and English;
- the guideline of the American College of Physicians (Qaseem 2017).

The information from these guidelines has been supplemented by information from systematic reviews which were sometimes also the basis for these guidelines, and with sources from reference lists from these guidelines and sources of these reviews. In addition, a systematic search was conducted on recent systematic reviews (see A.1 'Introduction').
The systematic search was carried out on 14 April 2020 by an information specialist (J.W. Schoones, Leiden University Medical Centre) in PubMed, MEDLINE, Embase, Emcare, Web of Science and the Cochrane Library for the period 1 January 2015 to 14 April 2020. To be able to make pronouncements about the effectiveness of behaviour-oriented treatments that are administered by an exercise therapist or physical therapist, reviews were selected which specifically focus on RCTs and whereby treatment was primarily (≥ 50%) administered by an exercise therapist or physical therapist or other paramedical professional (in a team-based approach, if needed). Only RCTs that were largely (≥ 50%) conducted in a primary care setting or in an outpatient department of a hospital were eligible for inclusion. They also had to contain data about one or more of the following outcome variables: pain intensity, physical functioning, quality of life, cognitive behavioural variables (e.g. fear of movement, catastrophisation, modification of maladaptive behaviour), work-related outcomes or undesirable effects. Reviews were not suitable if the treatment in the experimental group consisted of information and advice and pain education, because this intervention has been discussed separately in C.1 'Information and advice and (pain) education'.

Results from the guidelines

The British (multidisciplinary) Guideline on Low Back Pain and Sciatica in Over 16s: Assessment and Management has been published by the National Institute for Health and Care Excellence (NICE) and focuses on low back pain with or without sciatica (De Campos 2017). The guideline investigated the cost-effectiveness of behaviour-oriented treatments with pain, physical activity, quality of life and psychological distress as the critical outcome measures. Important outcome measures were > 30 improvement of pain or physical activity, undesirable effects and healthcare costs. The guideline included 21 RCTs. The NICE guideline investigated mindfulness (3 RCTs), behavioural treatment (2 RCTs EMG biofeedback, 3 RCTs operant approach), cognitive therapy (3 RCTs), cognitive behavioural treatment (10 RCTs) and Acceptance and Commitment Therapy (0 RCTs). Three RCTs investigated exercise therapy in combination with cognitive behavioural treatment (2 RCTs) or behavioural therapy (1 RTC). Three RCTs investigated the cost-effectiveness of cognitive behavioural treatment. The treatments were administered by psychologists or professionals in the healthcare sector, such as general practitioners and physical therapists who had received additional training for this. The behaviour-oriented treatments in the RCTs were rarely investigated as monotherapy, but were generally part of a composite treatment with various elements. Almost all studies included patients both with and without sciatica. The length of the treatments varied from three weeks to one year. Control treatments consisted of sham behaviour-oriented treatments, usual care or waitlist. The guideline states that there is no convincing evidence for offering a specific behaviour-oriented treatment. There are, however, indications that these treatments have added value if they are combined with other forms of treatment, such as exercise therapy.
Furthermore, it can be assumed that cognitive behavioural therapy is cost-effective as part of a multidisciplinary programme or in combination with exercise therapy. There is little evidence for this last conclusion, but it has been considered here that undertreatment of patients with chronic pain and psychosocial stress may lead to greater healthcare utilisation and higher costs. The NICE guideline states that behaviour-oriented treatments by physical therapists and exercise therapists (psychologically informed physiotherapy) should primarily focus on patients with chronic pain and psychosocial stress and not on patients with psychological disorders.
The Belgian Clinical Guideline on Low Back Pain and Radicular Pain describes a multidisciplinary healthcare pathway for people with low back pain with or without radicular pain (Van Wambeke 2019). The guideline largely bases recommendations on the guideline that the NICE has published, but the developers of the guideline also conducted literature review themselves on existing pathways and systematic reviews. The guideline recommends considering cognitive behavioural therapy for treating low back pain (with or without radicular pain), but only as part of multimodal treatment with a supervised exercise programme. The strength of the recommendation was classified as weak and the evidentiary level as moderate to very low.
The guideline of the American College of Physicians (ACP) is intended for people with low back pain with or without radicular pain and symptomatic spinal stenosis (Qaseem 2017). The guideline investigated the effectiveness of, among other things, EMG feedback, behavioural therapy and cognitive behavioural therapy, solution-oriented therapy, coping techniques, imagination, relaxation therapy and mindfulness therapy which were systematically published in randomised studies and systematic reviews. For people with chronic low back pain (duration of complaints > 12 weeks), the following treatments are recommended: mindfulness aimed at stress reduction (moderate evidentiary value), progressive relaxation therapy, EMG feedback, operant therapy and cognitive behavioural therapy (low evidentiary value). No recommendations are formulated for people with complaints lasting less than 12 weeks.

The following table contains an overview of the characteristics of the selected guidelines.

Characteristics of the selected guidelines

Source	Patient selection	Duration of complaints	Last update	Discipline
British guideline (De Campos 2017)	low back pain with or without sciatica	entire spectrum	15 December 2015	multidisciplinary
Belgian guideline (Van Wambeke 2019)	low back pain with or without sciatica	entire spectrum	18 April 2016	multidisciplinary
American guide-line (Qaseem 2017)	low back pain with or without sciatica	entire spectrum	November 2016	physicians

Results from the reviews

The systematic search performed by the guideline panel for the period from 1 January 2015 to 14 April 2021 yielded 2,439 unique hits. After selecting by title and abstract (appendix C.3-2), 444 reviews remained. After examining the titles and summaries, 33 reviews remained, and after the complete examination of the reviews, eight remained (Baez 2018; Barbari 2019; Bostick 2017; Hajihasani 2019; Hall 2018; Mariano 2018; Van Erp 2019; Zhang 2019) (see appendix C.3-1 and C.3-3 for the flowchart and exclusion table of this process).
The references of the selected reviews were screened for potential reviews which were not identified with the systematic search. This did not yield any additional reviews. Three reviews had only selected RCTs where the behaviour-oriented treatments were administered by a physical therapist, one review was only about behaviour-oriented treatments that were not allowed to be administered by a psychologist, and four reviews had various professional caregivers involved. See appendix C.3-7 and appendix C.3-8 for the characteristics of the included studies and an overview of the evidentiary value and effectiveness per outcome measure.

Systematic reviews whereby the physical therapist administered the behaviour-oriented treatment
Hall (2018) included five studies in which the effectiveness of cognitive behavioural therapy was investigated in patients with acute, subacute and chronic low back pain. In all studies, the experimental treatment was compared to another form of treatment (physical therapy, education, or advice on self-management and exercises). Treatments were administered in a group setting (2 RCTs), individually (2 RCTs) or individually in combination with group treatment (1 RCT); all treatments took place in a primary care setting. Four studies were eligible for a meta-analysis. Assessment of the evidentiary value was carried out according to the GRADE method. It appeared that cognitive behavioural therapy is more effective than control treatments for pain (SMD -0.21 [95% CI -0.33 to -0.09]) and for physical functioning (SMD -0.19 [95% CI -0.32 to -0.07]) in the long term (> 12 months) with a high evidentiary value. However, the effects were small and not clinically relevant. For quality of life there was no difference compared to control treatments (SMD -0.06 [95% CI -0.18 to 0.07]) in the long term with moderate evidentiary value.
Van Erp (2019) included five studies in which the effectiveness of a biopsychosocial approach was investigated in patients with chronic low back pain. In all studies, the experimental treatment was compared to another form of treatment (physical therapy, education and advice or manual therapy plus exercises). Treatments were administered individually (5 RCTs) or individually in combination

with group treatment (2 RCTs); all treatments took place in the primary care setting (7 RCTs). No meta-analysis was conducted. Assessment of the evidentiary value was carried out according to the GRADE method. The authors concluded that a biopsychosocial approach is more effective than only education/advice for pain and physical functioning in the short term (<3 months), medium term (3-12 months) and long term (>12 months) with moderate evidentiary value (n = 3). A biopsychosocial approach did not appear to be more effective than physically active treatments for pain and physical functioning in the short term, medium term and long term with a low evidentiary value (n = 4).
Zhang (2019) included 13 studies that investigated the effectiveness of a behaviour-oriented psychological approach that physical therapists used on patients with chronic LRP. Treatments were administered in the primary care setting (9 RCTs) and in the secondary care setting (4 RCTs). The experimental treatment was compared to usual care or waitlist (4 RCTs) and with an active treatment form (9 RCTs). In a meta-analysis that compared the experimental treatment with usual care or waitlist (4 RCTs), the experimental treatment was more effective in clinically relevant terms for pain in the short term (<6 months, SMD -0.33 [95% CI -0.50 to -0.15]), medium term (6-12 months, SMD -0.33 [95% CI -0.48 to -0.18]) and long term (>12 months, SMD -0.34 [95% CI -0.52 to -0.16]). In a second meta-analysis, which compared the experimental treatment with an active treatment (9 RCTs), the experimental treatment was only significantly more effective (but not in clinically relevant terms) for pain in the long term (> 12 months, SMD -0.18 [95% CI -0.35 to -0.01]).

Systematic reviews where a physical therapist or other paramedical professional administered the behaviour-oriented treatment in a large part of the studies (≥ 50%)
Bostick (2017) included 11 studies that investigated the effectiveness of psychologically oriented treatments that 'non-psychologists' administered to patients with acute, subacute and chronic LRP. The researchers concluded that psychological treatments administered by 'non-psychologists' have a slightly positive effect on low back pain and physical functioning.
Baez (2018) included five studies that investigated the effectiveness of cognitive functional or behavioural treatment and/or psychoeducation and/or fear-avoidance-based techniques for decreasing fear-avoidance beliefs and fear of movement in patients with acute, subacute and chronic LRP. Fear-avoidance beliefs are dysfunctional thoughts about pain and fear of pain, and kinesiophobia is an irrational fear of movement or fear of incurring injury again. Cognitive-functional treatment is aimed at training and integrating functional activities that a patient avoids in daily life. In two of the five RCTs, the researchers found significant and clinically relevant improvements in fear-avoidance beliefs in favour of cognitive behavioural treatments and/or psychoeducation. The researchers concluded that there was little and inconsistent evidence for the effectiveness of patient-oriented cognitive behavioural treatment and/or psychoeducation by rehabilitation specialists for treating fear-avoidance beliefs.
Barbari (2019) included 24 studies in which the effectiveness of communicative and educational strategies was investigated in patients with chronic LRP. The researchers concluded that cognitive behavioural treatment, pain education and graded exposure are the most effective treatments for changing (maladaptive) behaviour and compliance with exercises. Mindfulness-based stress reduction, graded activity and treatments aimed at self-management and coaching are short-lasting or entirely ineffective.
Hajihasani (2019) included 10 studies in which the effectiveness of operant, respondent and cognitive treatment strategies plus physical therapy versus physical therapy was investigated in patients with chronic LRP. The researchers concluded that operant, respondent and cognitive

treatment strategies as a supplement to physical therapy may result in reduced pain and improved physical functioning and quality of life, but there were no indications that these approaches resulted in decreased depression.
Mariano (2018) included six studies in which the effectiveness of cognitive-behavioural therapy treatments was investigated in patients with subacute LRP (duration of complaints 7–12 weeks). The researchers found a large variety of practitioners, treatment methods and treatment duration and concluded that the effectiveness of cognitive behavioural treatments have not yet been adequately investigated in patients with SALRP.
The results of the eight reviews should be viewed with some restraint, because they all score a crucially low quality on AMSTAR 2 (Shea 2017) (see appendix C.3-5 and C.3-6 for the characteristics of the included studies and an overview of the evidentiary value and effectiveness per outcome measure).

Considerations

To answer the clinical question, other considerations were also included in the literature to recommendation process in addition to the literature. Together they determine the direction and strength of the recommendation.
The assessment of considerations and the explanation are provided in appendix C.3-4.

Outcome measures

The effectiveness of behaviour-oriented treatments is assessed in RCTs and systematic reviews to a significant extent based on decreasing pain and improving physical functioning. However, with a unilateral focus on pain and physical functioning, the effectiveness of this form of treatment may be underestimated and the mutual differences between treatment methods remain underneath the surface. With behaviour-oriented treatments, patients often indicate that they do not experience less pain or improved physical functioning, but that, for example, they are able to cope with the pain better, have accepted the situation and have made room for supportive thoughts and undertaking valuable actions. These changes in cognitions and behaviour can then lead to more movement and better therapy compliance, because barriers to moving have been reduced or eliminated.

Choice of treatment form

More knowledge as to whether a psychological factor can help a mediating or moderating variable better answer the question 'Which type of behaviour-oriented treatment is recommended for which patient?' (Lee 2015). A mediating variable influences the causal relationship between the treatment and the result. This means that a change of the mediating variable during a treatment influences the result, whereby the variable does or does not interact with the given treatment (Pincus 2011). Although more research is needed, there are indications that variables such as self-effectiveness, catastrophisation, fear of movement, psychological distress and thoughts about pain are important mediating variables (Lee 2015, 2016). Therapy results are then determined in part by the degree of change of these variables during the treatment. For example, exercise therapy can be effective for reducing pain in people in whom psychological distress decreases at the same time, but the same treatment has less or no effect in people in whom this is not the case. These finding substantiate the theory that various types of behaviour-oriented treatments via the same set of mediating variables lead to the same results and do not differ in effectiveness. This is also an explanation for the fact that various models have been developed for the way in

which psychological factors are connected with each other and influence each other. One of the models is the fear-avoidance model, which explains how catastrophisation can lead to fear-avoidance beliefs, physical dysfunction, depression and decreased (physical and mental) capacity (Vlaeyen 2000).
A psychological factor can also be a moderating variable. A moderating variable specifies for which patient and under which conditions the treatment is effective. The moderating variable is measured at baseline and is specifically linked to the treatment given (Pincus 2011). Results of a systematic review suggest that fear of movement is a moderating variable (Wertli 2014). For example, for patients with short-term complaints (<6 months), there is moderate evidentiary value that treatments for reducing fear of movement in patients with fear of movement are more effective at baseline than treatments that do not pay specific attention to this (Wertli 2014). The same authors found less consistent results with a low evidentiary value for patients with long-term complaints (> 6 months). The authors explain this difference with the fact that they expect cognitions and behaviour in patients with longer-lasting complaints to be more difficult to change than in patients with short-lasting complaints. The authors suggest that training programmes with specific attention paid to fear of movement are unnecessary for patients without fear of movement or with low scores for fear of movement.

Implementation

Implementation of behaviour-oriented treatments may be impeded by a lack of knowledge about the possibilities of behaviour-oriented programmes among some clinicians (Kunstler 2018), the lack of skills to apply these treatment methods and the lack of full acceptance and integration of the biopsychosocial model in therapeutic actions (Kunstler 2018; Louw 2021). The physical therapy and exercise therapy basic training teaches the principles of the time-contingent approach, motivational interviewing and coaching for behavioural change. Nevertheless, the average physical therapist and exercise therapist experience a lack of skills and confidence as a hindrance to successfully offering behaviour-oriented treatments and indicate that additional training is needed (Hutting 2020; Synnott 2015). Keefe (2018) states that it is unclear how therapists should be trained in behaviour-oriented approaches and which competencies a psychosomatic therapist needs to possess.
There are very extensive professional profiles for Dutch psychosomatic physical therapists and exercise therapists. However, it is not possible from a practical viewpoint to train all physical therapists and exercise therapists as psychosomatic therapists. The need for additional training also depends on the setting in which the therapist works. In the secondary and tertiary care setting there is often support from psychosomatic therapists, social workers and psychologists, who can perform a significant part of the behaviour-oriented treatments and can assist and coach therapists. This support is often lacking in the primary care setting. There are also certain types of behaviour-oriented treatment that require considerably more training (e.g. cognitive behavioural therapy) or less training (e.g. Jacobson's progressive muscle relaxation technique).
Implementation of behaviour-oriented treatment can also be impeded if the patient's expectations do not correspond to the way the therapist approaches the complaints. The patient may be convinced that the back pain can only be explained based on the biomechanical model and/or strongly believe in the vulnerability of the back and that it needs to be protected. Although such thoughts can be a good reason for pain education and behaviour-oriented treatment, they can be very dominant and prevent the application of a biopsychosocial approach. The practitioner must take into account that patients can react negatively and sometimes even aggressively to the

suggestion that the complaints can be explained based on the biopsychosocial model and treated with a behaviour-oriented treatment. With such defensive reactions, it is important to be open to the patient's emotions and thoughts and to acknowledge these. Through empathetic listening and by asking questions, the patient's trust can be gained and a treatment plan can be developed that is agreeable to both stakeholders (Holt 2018).

Correlation between pain and the various biological, psychological and social factors

The degree of complexity and dominance of psychosocial factors determine, together with pain, general health status and context, the degree to which cognitive behavioural therapy is administered. To this end, the therapist must examine to what extent psychological factors are connected to other possible causes of pain. Tousignant-Laflamme (2017) and Walton (2018) classify five causes (drivers) of pain: 1) cognitive-emotional (e.g. pain-avoidant or pain-persistent), 2) nociceptive (active or imminent tissue damage, e.g. as a result of very low (physical and mental) capacity or disrupted motor control), 3) nervous system disruptions (e.g. neuropathic pain and pain resulting from central sensitisation), 4) comorbidity and 5) contextual (e.g. limited financial resources and low job satisfaction).

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Note C.4.1 Mobilisations and manipulations

Literature

To answer the clinical question, a systematic literature analysis was carried out for the following research question (PICO):

- What are the desirable and undesirable effects (O) of manipulation and/or mobilisation as a supplement to exercise therapy (I) versus exercise therapy possibly in combination with another control intervention without manipulation and/or mobilisation (C) in patients with low back pain with or without sciatica, without important warning signs (P)?
- What are the desirable and undesirable effects (O) of manipulation and/or mobilisation (I) versus a control intervention without manipulation and/or mobilisation (C) in patients with low back pain with or without sciatica, without important warning signs (P)?
- What are the desirable and undesirable effects (O) of manipulation (I) versus mobilisation (C) in patients with low back pain with or without sciatica, without important warning signs (P)?

Search

The literature review was conducted in a hierarchical manner; the search first focused on existing systematic reviews, possibly as part of an evidence-based guideline. Based on this search, the following sources were identified: a guideline of the National Institute for Health and Care Excellence (NICE) (De Campos 2017), the guideline of the Danish Health Authority (Stochkendahl 2018), a systematic review as a preliminary publication of a Cochrane review on chronic low back pain (Rubinstein 2019) and a Cochrane review on acute and subacute low back pain that is in its final phase (de Zoete). See the following table.

Selected guidelines and systematic reviews

Source	Patient selection	Duration of complaints	Last update
British guideline (NICE)	low back pain with or without sciatica	entire spectrum	15 December 2015
Danish guideline	low back pain with or without sciatica	<12 weeks	low back pain March 2016 sciatica December 2014
systematic review of chronic pain (Cochrane preliminary publication)	low back pain with or without sciatica (excluding studies with solely patients with sciatica)	>3 months	4 May 2018
systematic review of acute/ subacute pain (in the final phase at the time of this guideline's development)	low back pain with or without sciatica (excluding studies with solely patients with sciatica)	0 to 12 weeks	4 May 2018

The literature review of the two systematic reviews was from a more recent date than that of the two guidelines but had excluded studies with solely patients with sciatica. These studies had been included in the British and Danish guidelines, due to which these guidelines were better aligned with our search. Ultimately, we decided to use the two reviews as basic principles for selecting articles and implement an update of the search starting on 1 January 2018. Finally, the NICE guideline and the Danish guideline were screened for additional literature with specific attention paid to studies where solely patients with sciatica were selected.
The articles from the two systematic reviews and the two guidelines were tested according to the predefined inclusion criteria. See the following table.

Selection criteria for the search on literature about manipulation and mobilisation

Type of studies	Randomised controlled study published in English or Dutch
Type of patients	Adults with low back pain with or without sciatica, without important warning signs (see A.1 'Introduction')
Type of intervention	**PICO 1:** mobilisation and/or manipulation as a supplement to exercise therapy (with exercise therapy being an important part of the treatment [>50% of the treatment time]) **PICO 2:** mobilisation and/or manipulation **PICO 3:** mobilisation versus manipulation Mobilisation and manipulation are understood to mean passive hands-on treatment techniques on the spine. Mobilisation is a low-speed movement technique with minor or major movement results within the patient's range of motion and within the patient's control. Manipulation is a movement technique whereby local force is applied with high speed and low amplitude on a specific lumbar segment on or just before the passive or physiological end position of the joint.
Type of comparison	**PICO 1:** Control intervention consisting of exercise therapy, possibly in combination with another control intervention pursuant to the current guideline without manipulation and/or mobilisation **PICO 2:** Control intervention: a) intervention pursuant to the current guideline; b) sham mobilisation or manipulation; c) placebo treatment; d) no treatment (do nothing/wait list) Interventions pursuant to this guideline are: information and advice and (pain) education, exercise therapy, cognitive behavioural treatment, manipulation/ mobilisation, massage, dry needling, kinesiotaping, interference and TENS. Interventions that are not pursuant to this guideline include supervision by a general practitioner, operations, epidural, facet blockage/injections, acupuncture, kinesiology and pain medication, among others. **Exclusion:** mobilisation and/or manipulation combined with interventions that are not pursuant to the current guideline, mobilisation and/or manipulation combined with another intervention, due to which the value of the mobilisation and/or manipulation cannot be extracted (e.g. mobilisation and/or manipulation plus electrotherapy vs. exercise therapy), mobilisation and/or manipulation combined with specific techniques (e.g. spinal mobilisation with leg movement), the control intervention consists of mobilisation and/or manipulation, the data of the patients with low back pain cannot be separately extracted, are missing from follow-up measurements, practitioners do not have (para)medical training (e.g. napropaths and bone setters), strong bias in the research (e.g. only patients who respond well to mobilisation and/or manipulation were selected), the data cannot be derived from the article and the author does not respond to a request to deliver these and specific patient populations with low back pain (e.g. after pregnancy).

Type of outcome	**Crucial:** Pain intensity. Measurement instruments for pain include the Visual Analogue Scale (VAS) and the Numeric Pain Rating Scale (NPRS). Physical functioning. Measurement instruments for physical functioning in patients with low back pain include the Roland-Morris Disability Questionnaire (RMDQ), Oswestry Disability Index (ODI) and Quebec Back Pain Disability Scale (QBPDS) and physical functioning on a VAS. **Important:** Quality of life. Measurement instruments for quality of life include the SF-36, EuroQol, and general experienced quality of life on a VAS. Work-related outcomes. Measurement instruments may be aimed at the degree of return to paid work or change in work productivity, for example. Undesirable effects. All negative effects that might be related to the intervention. This may include increased pain and/or limitations in physical functioning, or pain and/or limitations in physical functioning of a type other than the kind for which one initially sought help, occurring immediately after the intervention. The effects can be short-term, but also serious or even life-threatening, or can result in hospitalisation.
Type of timeline	Short (≤4 months) and/or long (>4 months) term. In the event of multiple measurement points, the measurement point that is closest to this time indication is included.

Selection of studies from systematic reviews and guidelines

The systematic review of patients with chronic low back pain (Rubinstein 2019) entailed 47 RCTs, of which 31 fulfilled our inclusion criteria (Balthazard 2012; Bialosky 2014; Bronfort 2011; Castro-Sánchez 2016; Cecchi 2010; Cook 2013; Dougherty 2014; Ferreira 2007; Ghroubi 2007; Gibson 1985; Goldby 2006; Hidalgo 2015; Hondras 2009; Hsieh 2002; Koes 1992; Krekoukias 2017; Paatelma 2008; Petersen 2011; Pope 1994, Postacchini 1988; Rasmussen-Barr 2003; Rasmussen 2008; Sarker 2016; Senna 2011; Team 2004; Ulger 2017; Vismara 2012; Waagen 1986; Walker 2013; Waqqar 2016; Xia 2016).
The systematic review of patients with acute] and subacute low back pain (De Zoete, not published) entailed 31 RCTs, of which 17 fulfilled our inclusion criteria (Brennan 2006; Cherkin 1998; Childs 2004; Cleland 2009; Glover 1974; Hadler 1987; Hallegraeff 2009; Hoehler 1981; Hurley 2004; Hussain 2013; MacDonald 1990; Postacchini 1988; Schenk 2012; Seferlis 1998; Shah 2016; Skargren 1997; Wreje 1992). One article was included in both studies (Postacchini 1988), so that the total number of selected articles from the two reviews was 47 articles.
The search in the NICE guideline yielded four additional articles (Bronfort 2014; Morton 1999; Santilli 2006; Triano 1995), and a more indepth analysis of the Danish guideline yielded zero additional articles.
On 4 June 2020, an information specialist (J.W. Schoones, Leiden University Medical Centre) conducted a systematic search in PubMed, MEDLINE, Embase, Emcare, Web of Science and the Cochrane Library for the period 1 January 2018 to 4 June 2020 (see appendix C.4.1-6 for the search rationale). The update of the systematic search produced 462 unique hits. After screening of the title and the abstract based on the inclusion criteria, 449 articles were excluded. The complete article was screened for 13 articles, and six studies turned out to fulfil our criteria (Alt 2020; De Oliveira Meirelles 2020; Ford 2019; Grande-Alonso 2019; Sarker 2019; Schulz 2019). See appendix C.4.1-1 for the flowchart of the inclusion process.
The total number of studies in this literature analysis therefore amounts to 57. See appendix C.4.1-3 for the flowchart of the inclusion process. The studies that were excluded from the updated search and the two systematic reviews are listed in appendix C.4.1-2.

Characteristics of the included studies

The 57 included studies included a total of 8,646 patients with low back pain, with a median number of patients per study of 109 (IQR 58–199). Most studies included patients of middle age (35–60 years), with and without sciatica. Four studies included only patients with low back pain without sciatica (Dougherty 2014; Ghroubi 2007; Sarker 2019; Shah 2016) and two studies only patients with sciatica (Bronfort 2014; Santilli 2006). In total, 37 studies included only or primarily patients with chronic low back pain, 19 studies included only or primarily patients with acute or subacute pain and one study included patients with acute, subacute and chronic low back pain (Postacchini 1988). The practitioners in the studies were physical therapists or manual therapists (24 studies), chiropractors (16 studies), osteopaths (6 studies), physicians (3 studies) or practitioners with a different background (3 studies). In 5 studies the practitioner's background was unclear.

Individual study quality (RoB)

The quality of the design and execution of the individual studies (risk of bias, RoB) was assessed with the help of the Cochrane Risk-of-Bias tool (Higgins 2011). The assessments were taken over from the Cochrane reviews; the studies that did not appear in the two reviews were assessed by AA. An overview of the study quality assessment (RoB) per study is provided in appendix C.4.1-4.

Effectiveness and evidentiary value of mobilisation and/or manipulation plus exercise therapy versus exercise therapy (plus another intervention)

The effect of mobilisation and/or manipulation plus exercise therapy on pain and physical limitations in the short term was compared in 11 RCTs (Balthazard 2012; Bronfort 2014; Childs 2004; Grande-Alonso 2019; MacDonald 1990; Morton 1999; Petersen 2011; Rasmussen 2008; Schulz 2019; Team 2004; Vismara 2012) with exercise therapy alone or with the effect of exercise therapy plus another intervention aligned with the guideline, and in the long term in seven RCTs (Balthazard 2012; Bronfort 2014; Childs 2004; Petersen 2011; Rasmussen 2008; Schulz 2019; Team 2004).
An overview of the results in the short term and long term that could be pooled is depicted in the following tables. See appendix C.4.1-7, figures 1 through 4 for the forest plots of the crucial and important outcomes.

GRADE evidence profile of the studies on mobilisation and/or manipulation plus exercise therapy versus exercise therapy (plus another intervention) in the short term (≤4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	Effects (crucial or important)
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Pain (NPRS [0-100] and VAS [0-100])										
9	severe[1]	severe[2]	not severe	not severe	not determined	776	739	MD -6.66 (-11.04; -2.29)	low	crucial
Physical functioning (ODI, RMDQ)										
10	severe[1]	severe[2]	not severe	severe[4]	not determined	863	830	SMD -0.15 (-0.36; 0.05)	very low	crucial
Quality of life (SF-36; PCS 0-100)										
3	severe[1]	not severe	not severe	not severe	not determined	407	447	MD 0.08 (-0.93; 1.09)	moderate	important

Quality of life (SF-36, MCS 0-100)										
3	severe[1]	not severe	not severe	not severe	not determined	407	447	MD 0.75 (-0.27; 1.76)	moderate	important
Quality of life (EuroQol, VAS 0-100)										
2	severe[1]	severe[2]	not severe	severe[4]	not determined	191	232	MD 3.81 (-3.44; 11.05)	very low	important
Work-related outcomes (number of patients with work restrictions (not further operationalised))*										
1	severe[1]	not severe	severe[3]	severe[5]	not determined	32 / 47	35 / 65	RR 1.26 (0.94; 1.70)	very low	important
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; *n* = number; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RMDQ = Roland Morris Disability Questionnaire; RoB = risk of bias; RR = risk ratio; SF-36 = 36-Item Short Form Health Survey; SMD = standardized mean difference; VAS = Visual Analogue Scale.

[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 1 level due to unexplained heterogeneity (CIs do not overlap, I2> 60% and/or tau2 *p* <0.10). [3] Down-graded by 1 level due to the varied and imprecise descriptions of the measurement methods. [4] Down-graded by 1 level because the 95% CI exceeds no effect and a clinically relevant effect (broad confidence interval). [5] Down-graded by 1 level due to a sample size <300.

Note: Outcomes are in favour of the intervention mobilisation/manipulation with a decrease in pain and physical functioning and with an increase in quality of life and with an RR >1.00.

* Patients (*n*) with work-related outcomes: the number of patients that could work again compared to the number of patients that could not work at baseline due to low back pain.

GRADE evidence profile of the studies on mobilisation and/or manipulation plus exercise therapy versus exercise therapy (plus another intervention) in the long term (> 4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	Effects (crucial or important)
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Pain (NPRS [0-100] and VAS [0-100])										
6	severe[1]	not severe	not severe	not severe	not determined	711	671	MD -0.33 (-2.32; 1.66)	moderate	crucial
Physical functioning (ODI, RMDQ)										
6	severe[1]	severe[2]	not severe	severe[4]	not determined	765	719	SMD -0.18 (-0.38; 0.03)	very low	crucial
Quality of life (SF-36; PCS 0-100)										
3	severe[1]	not severe	not severe	not severe	not determined	397	450	MD -0.03 (-1.22; 1.16)	moderate	important
Quality of life (SF-36, MCS 0-100)										
3	severe[1]	not severe	not severe	not severe	not determined	397	450	MD 1.40 (0.30; 2.51)	moderate	important
Quality of life (EuroQol, VAS 0-100)										
1	severe[1]	not severe	not severe	severe[5]	not determined	154	167	MD -3.84 (-8.51; 0.83)	low	important

Work-related outcomes (number of patients with work restrictions (not further operationalised))*										
2	severe[1]	severe[2]	severe[3]	severe[5]	not determined	80 / 99	76 / 106	RR 1.12 (0.94; 1.33)	very low	important
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; *n* = number; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RMDQ = Roland Morris Disability Questionnaire; RoB = risk of bias; RR = risk ratio; SF-36 = 36-Item Short Form Health Survey; SMD = standardized mean difference; VAS = Visual Analogue Scale.

[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 1 level due to unexplained heterogeneity (CIs do not overlap, I2> 60% and/or tau2 *p* <0.10). [3] Down-graded by 1 level due to the varied and imprecise descriptions of the measurement methods. [4] Down-graded by 1 level because the 95% CI exceeds no effect and a clinically relevant effect (broad confidence interval). [5] Down-graded by 1 level due to a sample size <300 with dichotomous outcome measures and <400 with continuous outcome measures.

Note: Outcomes are in favour of the intervention mobilisation/manipulation with a decrease in pain and physical functioning and with an increase in quality of life and with an RR >1.00.

* Patients (*n*) with work-related outcomes: the number of patients that could work again compared to the number of patients that could not work at baseline due to low back pain

Effectiveness and evidentiary value of mobilisation and/or manipulation versus another intervention

The effect of mobilisation and/or manipulation on pain and physical limitations in the short term was compared with another intervention aligned with the guideline in 21 RCTs (Brennan 2006; Bronfort 2011; Cecchi 2010; Cherkin 1998; De Oliveira Meirelles 2020; Dougherty 2014; Ferreira 2007; Ford 2019; Hsieh 2002; Hurley 2004; Krekoukias 2017; Paatelma 2008; Rasmussen-Barr 2003; Sarker 2016; Schenk 2012; Shah 2016; Skargren 1997; Team 2004; Triano 1995; Ulger 2017; Waqqar 2016), and in the long term in 12 RCTs (Brennan 2006; Bronfort 2011; Cecchi 2010; Dougherty 2014; Ferreira 2007; Ford 2019; Hsieh 2002; Hurley 2004; Paatelma 2008; Rasmussen-Barr 2003; Skargren 1997; Team 2004). An overview of the results in the short term and long term that could be pooled is depicted in the following tables. See appendix C.4.1-7 for the forest plots of the crucial and important outcomes (figures 5 through 8).

GRADE evidence profile of the studies on mobilisation and/or manipulation versus another intervention in the short term (≤4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	Effects (crucial or important)
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Pain (NPRS [0-100] and VAS [0-100])										
25	severe[1]	severe[3]	not severe	not severe	not determined	1391	1552	MD -5.75 (-10.62; -0.89)	low	crucial
Physical functioning (ODI, RMDQ)										
20	severe[1]	severe[3]	not severe	severe[4]	not determined	1352	1616	SMD -0.18 (-0.36; -0.01)	low	crucial

Quality of life (SF-36; PCS 0-100)										
2	very severe[2]	not severe	not severe	not severe	not determined	357	375	MD -0.24 (-1.30; 0.83)	low	important
Quality of life (SF-36, MCS 0-100)										
2	very severe[2]	not severe	not severe	not severe	not determined	357	375	MD 2.17 (1.05; 3.29)	low	important
Quality of life (EuroQol, VAS 0-100)										
5	very severe[2]	not severe	not severe	not severe	not determined	342	308	MD 2.51 (-0.12; 5.13)	low	important
Work-related outcomes (number of patients with work restrictions (not further operationalised))*										
2	very severe[2]	not severe	severe[4]	severe[5]	not determined	41 / 94	56 / 105	RR 0.94 (0.71; 1.27)	very low	important
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; *n* = number; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RMDQ = Roland Morris Disability Questionnaire; RoB = risk of bias; RR = risk ratio; SF-36 = 36-Item Short Form Health Survey; SMD = standardized mean difference; VAS = Visual Analogue Scale.
[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 2 levels due to severe RoB on other categories, whereby studies with many participants outweigh studies with few participants.
[3] Down-graded by 1 level due to unexplained heterogeneity (CIs do not overlap, I2> 60% and/or tau2 *p* <0.10). [4] Down-graded by 1 level due to the varied and imprecise descriptions of the measurement methods. [5] Down-graded by 1 level due to a sample size <300 with dichotomous outcome measures and <400 with continuous outcome measures.
Note: Outcomes are in favour of the intervention mobilisation/manipulation with a decrease in pain and physical functioning and with an increase in quality of life and with an RR >1.00.
* Patients (*n*) with work-related outcomes: the number of patients that could work again compared to the number of patients that could not work at baseline due to low back pain.

GRADE evidence profile of the studies on mobilisation and/or manipulation versus another intervention in the long term (> 4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	Effects (crucial or important)
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Pain (NPRS [0-100] and VAS [0-100])										
11	severe[1]	severe[3]	not severe	not severe	not determined	950	1119	MD -2.40 (-5.72; 0.92)	low	crucial
Physical functioning (ODI, RMDQ)										
12	severe[1]	severe[3]	not severe	not severe	not determined	1000	1218	SMD -0.10 (-0.22; 0.02)	low	crucial
Quality of life (SF-36; PCS 0-100)										
2	not severe	not severe	not severe	not severe	not determined	344	373	373 MD -0.61 (-1.88; 0.67)	low	important

Quality of life (SF-36, MCS 0-100)										
2	very severe[2]	not severe	not severe	not severe	not determined	344	373	MD 1.11 (-0.28; 2.51)	low	important
Quality of life (EuroQol, VAS 0-100)										
4	very severe[2]	severe[3]	not severe	not severe	not determined	276	245	MD -1.76 (-4.92; 1.41)	very low	important
Work-related outcomes (number of patients with work restrictions (not further operationalised))*										
2	very severe[2]	not severe	severe[4]	severe[5]	not determined	48 / 94	59 / 105	RR 1.03 (0.79; 1.35)	very low	important
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; *n* = number; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RMDQ = Roland Morris Disability Questionnaire; RoB = risk of bias; RR = risk ratio; SF-36 = 36-Item Short Form Health Survey; SMD = standardized mean difference; VAS = Visual Analogue Scale.

[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 2 levels due to severe RoB on other categories, whereby studies with many participants outweigh studies with few participants.

[3] Down-graded by 1 level due to unexplained heterogeneity (CIs do not overlap, I2> 60% and/or tau2 *p* <0.10). [4] Down-graded by 1 level due to the varied and imprecise descriptions of the measurement methods. [5] Down-graded by 1 level due to a sample size <300 with dichotomous outcome measures and <400 with continuous outcome measures.

Note: Outcomes are in favour of the intervention mobilisation/manipulation with a decrease in pain and physical functioning and with an increase in quality of life and with an RR >1.00.

* Patients (*n*) with work-related outcomes: the number of patients that could work again compared to the number of patients that could not work at baseline due to low back pain.

Effectiveness and evidentiary value of mobilisation and/or manipulation versus sham mobilisation and/or manipulation

The effect of mobilisation and/or manipulation on pain and physical limitations in the short term was compared with sham mobilisation and/or manipulation in 8 RCTs (Bialosky 2014; Ghroubi 2007; Hidalgo 2015; Krekoukias 2017; Santilli 2006; Senna 2011; Triano 1995; Waagen 1986), and in the long term in two RCTs (Santilli 2006; Senna 2011).

An overview of the results in the short term and long term that could be pooled is depicted in the following tables. See appendix C.4.1-7 for the forest plots of the crucial and important outcomes (figures 9 through 11).

GRADE evidence profile of the studies on mobilisation and/or manipulation versus sham mobilisation and/or manipulation in the short term (≤4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	Effects (crucial or important)
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Pain (NPRS [0-100] and VAS [0-100])										
8	severe[1]	severe[3]	not severe	severe[4]	not determined	231	262	MD -10.22 (-25.34; 4.90)	very low	crucial
Physical functioning (ODI, RMDQ)										
5	severe[1]	severe[3]	not severe	severe[5]	not determined	134	173	SMD -0.77 (-1.59; 0.04)	very low	crucial

Quality of life (SF-36; PCS 0-100)										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	important
Quality of life (SF-36, MCS 0-100)										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	important
Kwaliteit van leven (EuroQol, VAS 0-100)										
1	very severe[2]	not severe	not severe	severe[5]	not determined	26	37	SMD 0.35 (-0.16; 0.85)	very low	important
Work-related outcomes (number of patients with work restrictions (not further operationalised))*										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	important
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; *n* = number; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RMDQ = Roland Morris Disability Questionnaire; RoB = risk of bias; RR = risk ratio; SF-36 = 36-Item Short Form Health Survey; SMD = standardized mean difference; VAS = Visual Analogue Scale.

[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 2 levels due to severe RoB on other categories, whereby studies with many participants outweigh studies with few participants.

[3] Down-graded by 1 level due to unexplained heterogeneity (CIs do not overlap, I2> 60% and/or tau2 *p* <0.10). [4] Down-graded by 1 level because the 95% CI exceeds no effect and a clinically relevant effect (broad confidence interval). [5] Down-graded by 1 level due to a sample size <300 with dichotomous outcome measures and <400 with continuous outcome measures.

Note: Outcomes are in favour of the intervention mobilisation/manipulation with a decrease in pain and physical functioning and with an increase in quality of life and with an RR >1.00.

* Patients (*n*) with work-related outcomes: the number of patients that could work again compared to the number of patients that could not work at baseline due to low back pain.

GRADE evidence profile of the studies on mobilisation and/or manipulation versus sham mobilisation and/or manipulation in the long term (> 4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	Effects (crucial or important)
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Pain (NPRS [0-100] and VAS [0-100])										
2	very severe[2]	severe[3]	not severe	severe[4]	not determined	74	85	MD -3.93 (-15.84; 7.99)	very low	crucial
Physical functioning (ODI, RMDQ)										
1	severe[1]	not severe	not severe	severe[4]	not determined	26	37	SMD -0.25 (-0.76; 0.25)	low	crucial
Quality of life (SF-36; PCS 0-100)										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	important

Quality of life (SF-36, MCS 0-100)										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	important
Quality of life (EuroQol, VAS 0-100)										
1	very severe[2]	not severe	not severe	severe[4]	not determined	26	37	SMD -0.25 (-0.76; 0.25)	very low	important
Work-related outcomes (number of patients with work restrictions (not further operationalised))*										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	important
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; *n* = number; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RMDQ = Roland Morris Disability Questionnaire; RoB = risk of bias; RR = risk ratio; SF-36 = 36-Item Short Form Health Survey; SMD = standardized mean difference; VAS = Visual Analogue Scale.
[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 2 levels due to severe RoB on other categories, whereby studies with many participants outweigh studies with few participants.
[3] Down-graded by 1 level due to unexplained heterogeneity (CIs do not overlap, I2> 60% and/or tau2 *p* <0.10). 4 Down-graded by 1 level due to a sample size <300 with dichotomous outcome measures and <400 with continuous outcome measures.
Note: Outcomes are in favour of the intervention mobilisation/manipulation with a decrease in pain and physical functioning and with an increase in quality of life and with an RR >1.00.
* Patients (*n*) with work-related outcomes: the number of patients that could work again compared to the number of patients that could not work at baseline due to low back pain.

Effectiveness and evidentiary value of mobilisation and/or manipulation versus placebo

The effect of mobilisation and/or manipulation on pain and physical limitations in the short term was compared to placebo in two RCTs (Gibson 1985; Walker 2013). No RCTs were found that studied the effect on pain and/or physical functioning in the long term.

An overview of the results in the short term that could be pooled is depicted in the following table. See appendix C.4.1-7 for the forest plots of the crucial and important outcomes (figures 12 through 14).

GRADE evidence profile of the studies on mobilisation and/or manipulation versus placebo in the short term (≤4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	Effects (crucial or important)
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Pain (NPRS [0-100] and VAS [0-100])										
2	severe[1]	not severe	not severe	severe[4]	not determined	111	123	MD -1.96 (-7.46; 3.53)	low	crucial
Physical functioning (ODI, RMDQ)										
1	severe[1]	not severe	not severe	severe[4]	not determined	91	92	SMD -0.33 (-0.62; -0.04)	low	crucial

Quality of life (SF-36, PCS 0-100)										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	impor-tant
Quality of life (SF-36, MCS 0-100)										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	impor-tant
Quality of life (EuroQol, VAS 0-100)										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	impor-tant
Work-related outcomes (number of patients with work restrictions (not further operationalised))*										
1	very severe[2]	not severe	severe[3]	severe[4]	not deter-mined	4 / 6	11 / 17	RR 1.03 (0.53; 2.01)	very low	impor-tant
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; *n* = number; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RMDQ = Roland Morris Disability Questionnaire; RoB = risk of bias; RR = risk ratio; SF-36 = 36-Item Short Form Health Survey; SMD = standardized mean difference; VAS = Visual Analogue Scale.

[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 2 levels due to severe RoB on other categories, whereby studies with many participants outweigh studies with few participants.

[3] Down-graded by 1 level due to the varied and imprecise descriptions of the measurement methods. [4] Down-graded by 1 level due to a sample size <300 with dichotomous outcome measures and <400 with continuous outcome measures.

Note: Outcomes are in favour of the intervention mobilisation/manipulation with a decrease in pain and physical functioning and with an increase in quality of life and with an RR >1.00.

* Patients (*n*) with work-related outcomes: the number of patients that could work again compared to the number of patients that could not work at baseline due to low back pain.

Effectiveness and evidentiary value of mobilisation and/or manipulation versus no treatment

The effect of mobilisation and/or manipulation on pain and physical limitations in the short term was compared to no treatment in two RCTs (Bialosky 2014; Xia 2016). No RCTs were found that studied the effect on pain and/or physical functioning in the long term.

An overview of the results in the short term that could be pooled is depicted in the following table. See appendix C.4.1-7 for the forest plots of the crucial and important outcomes (figures 15 through 16).

GRADE evidence profile of the studies on mobilisation and/or manipulation versus no treatment in the short term (≤4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	Effects (crucial or important)
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Pain (NPRS [0-100] and VAS [0-100])										
2	severe[1]	severe[2]	not severe	severe[3]	not deter-mined	156	70	MD -8.42 (-20.90; 4.05)	very low	crucial

Physical functioning (ODI, RMDQ)										
2	severe[1]	not severe	not severe	severe[3]	not determined	143	70	SMD −0.70 (−1.02; −0.39)	low	crucial
Quality of life (SF-36, PCS 0-100)										
1	severe[1]	not severe	not severe	severe[3]	not determined	129	42	MD 4.95 (3.20; 6.71)	low	important
Quality of life (SF-36, MCS 0-100)										
1	severe[1]	not severe	not severe	severe[3]	not determined	129	42	MD 0.35 (−1.57; 2.27)	low	important
Quality of life (EuroQol, VAS 0-100)										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	important
Work-related outcomes (number of patients with work restrictions (not further operationalised))*										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	important
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RMDQ = Roland Morris Disability Questionnaire; RoB = risk of bias; RR = risk ratio; SF-36 = 36-Item Short Form Health Survey; SMD = standardized mean difference; VAS = Visual Analogue Scale.

[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 1 level due to unexplained heterogeneity (CIs do not overlap, I2> 60% and/or tau2 p <0.10). [3] Down-graded by 1 level due to a sample size <300 with dichotomous outcome measures and <400 with continuous outcome measures.

Note: Outcomes are in favour of the intervention mobilisation/manipulation with a decrease in pain and physical functioning and with an increase in quality of life and with an RR >1.00.

* Patients (*n*) with work-related outcomes: the number of patients that could work again compared to the number of patients that could not work at baseline due to low back pain.

Effectiveness and evidentiary value of manipulation versus mobilisation

The effect of manipulation on pain and physical limitations in the short term was compared to mobilisation in 6 RCTs (Castro-Sánchez 2016; Cleland 2009; Cook 2013; Hadler 1987; Hondras 2009; Xia 2016) and in the long term in two RCTs (Cleland 2009; Hondras 2009).

An overview of the results in the short term and long term that could be pooled is depicted in the following tables. See appendix C.4.1-7 for the forest plots of the crucial and important outcomes (figures 17 through 20).

GRADE evidence profile of the studies on manipulation versus mobilisation in the short term (≤4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	Effects (crucial or important)
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Pain (NPRS [0-100] and VAS [0-100])										
5	severe[1]	severe[2]	not severe	severe[3]	not determined	320	327	MD −4.46 (−11.86; 2.94)	very low	crucial

Physical functioning (ODI, RMDQ)										
6	severe[1]	severe[2]	not severe	severe[3]	not determined	352	357	SMD −0.33 (−0.96; 0.30)	very low	crucial
Quality of life (SF-36, PCS 0-100)										
1	severe[1]	not severe	not severe	severe[4]	not determined	63	66	MD −0.30 (−2.60; 2.00)	low	important
Quality of life (SF-36, MCS 0-100)										
1	severe[1]	not severe	not severe	severe[4]	not determined	63	66	MD −1.90 (−4.40; 0.60)	low	important
Quality of life (EuroQol, VAS 0-100)										
1	severe[1]	not severe	not severe	severe[4]	not determined	31	31	MD 2.20 (−6.79; 11.19)	low	important
Work-related outcomes (number of patients with work restrictions (not further operationalised))*										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	important
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; *n* = number; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RMDQ = Roland Morris Disability Questionnaire; RoB = risk of bias; RR = risk ratio; SF-36 = 36-Item Short Form Health Survey; SMD = standardized mean difference; VAS = Visual Analogue Scale.

[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 1 level due to unexplained heterogeneity (CIs do not overlap, I2> 60% and/or tau2 *p* <0.10). [3] Down-graded by 1 level because the 95% CI exceeds no effect and one clinically relevant effect (broad confidence interval). [4] Down-graded by 1 level due to a sample size <300 with dichotomous outcome measures and <400 with continuous outcome measures.

Note: Outcomes are in favour of the intervention mobilisation/manipulation with a decrease in pain and physical functioning and with an increase in quality of life and with an RR >1.00.

* Patients (*n*) with work-related outcomes: the number of patients that could work again compared to the number of patients that could not work at baseline due to low back pain.

GRADE evidence profile of the studies on manipulation versus mobilisation in the long term (> 4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	Effects (crucial or important)
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Pain (NPRS [0-100] and VAS [0-100])										
1	severe[1]	not severe	not severe	severe[3]	not determined	65	66	MD −4.45 (−8.64; −0.26)	low	crucial
Physical functioning (ODI, RMDQ)										
2	severe[1]	severe[2]	not severe	severe[3]	not determined	154	152	SMD −0.49 (−1.24; 0.26)	very low	crucial
Quality of life (SF-36; PCS 0-100)										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	important

Quality of life (SF-36, MCS 0-100)										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	impor-tant
Quality of life (EuroQol, VAS 0-100)										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	impor-tant
Work-related outcomes (number of patients with work restrictions (not further operationalised))*										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	impor-tant
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; *n* = number; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RMDQ = Roland Morris Disability Questionnaire; RoB = risk of bias; RR = risk ratio; SF-36 = 36-Item Short Form Health Survey; SMD = standardized mean difference; VAS = Visual Analogue Scale.

[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 1 level due to unexplained heterogeneity (CIs do not overlap, I2> 60% and/or tau2 *p* <0.10). [3] Down-graded by 1 level due to a sample size <300 with dichotomous outcome measures and <400 with continuous outcome measures.

Note: Outcomes are in favour of the intervention mobilisation/manipulation with a decrease in pain and physical functioning and with an increase in quality of life and with an RR >1.00.

* Patients (*n*) with work-related outcomes: the number of patients that could work again compared to the number of patients that could not work at baseline due to low back pain.

Considerations

To answer the clinical question, other considerations were also included in the literature to recommendation process in addition to the literature. Together they determine the direction and strength of the recommendation. The assessment of considerations and the explanation are provided in appendix C.4.1-5.

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Note C.4.2 Massage

Literature

To answer the clinical question, a systematic literature analysis was carried out for the following research question (PICO):

> What are the desirable and undesirable effects (O) of massage as a supplement to exercise therapy (I) versus exercise therapy alone (C) in patients with low back pain with or without sciatica, without important warning signs (P)?
> Exercise therapy can be applied either alone or in combination with information and advice.

Based on the literature, the guideline panel selected 'pain' and 'physical functioning' as crucial outcome measures (Chiarotto 2015; ICHOM Working Group Members for Low Back Pain 2017; Verburg 2019).

Undesirable effects are all negative effects that may be related to the intervention (e.g. increased pain and/or limitations in physical functioning, or pain and/or limitations in physical functioning of a type other than the kind for which one initially sought help, occurring immediately after the intervention).

Search

The literature review was conducted in a hierarchical manner; the search first focused on existing systematic reviews, possibly as part of an evidence-based guideline (see A.1 'Introduction'). Based on this search, a literature review of the Cochrane Library about massage for low back pain was identified (Furlan 2015). Although massage is often used as a supplement to other interventions in physical therapy, this review compares the singular effect of massage with passive and active therapies. Studies whereby massage is combined with other interventions, such as exercise therapy, were excluded in this study. The review concerns an update of the literature review by the same authors from 2008 (Furlan 2008), which did include studies on the added value of massage on other therapies. In order to answer the clinical question about massage, the literature of both reviews was screened for our inclusion criteria, and the search of these systematic reviews was subsequently updated.

Selection of studies in the literature review of the Cochrane Library

For the literature review of the Cochrane Library (Furlan 2015), searches were conducted in MEDLINE, Embase, CENTRAL, CINAHL, LILACS, Index to Chiropractic Literature and Proquest Dissertation Abstracts up to August 2014. Reference lists were also screened. Screening of the table with characteristics of the excluded studies did not yield any articles which investigated the added value of massage on exercise therapy.
Furlan 2008 describes five studies that compare the added value of massage for other therapies with the other therapy alone (Franke 2000; Geisser 2005; Poole 2007; Preyde 2000; Yip 2004). These five studies were tested according to our predefined inclusion criteria. See the following table.

Selection criteria for the search on literature about the value of massage

Type of studies	Systematic review (possibly as a part of a guideline), published in English or Dutch
Type of patients	Adults with low back pain with or without sciatica, without important warning signs (see A.1 'Introduction')
Type of intervention	Massage as a supplement to exercise therapy, possibly combined with information and advice
Type of comparison	Exercise therapy, possibly combined with information and advice **Exclusion:** massage techniques aimed at energy pathways, such as acupressure, tuina, traditional Chinese massage, reiki, etc.
Type of outcome	At least one of the following outcome measures: **Desirable:** Crucial: pain, physical functioning **Undesirable:** all negative effects that might be related to the intervention
Type of timeline	Short (≤4 months) and/or long (>4 months) term. In the event of multiple measurement points, the measurement point that is closest to this time indication is used.

One of the studies fulfilled the inclusion criteria and was analysed (Preyde 2000). The articles that were excluded based on the complete text and the reason of the exclusion are listed in appendix C.4.2-2.
On 25 January 2021, an information specialist (J.W. Schoones, Leiden University Medical Centre) conducted a systematic search in PubMed, MEDLINE, Embase, Emcare, Web of Science and the Cochrane Library for updating of the Cochrane review from 2015 (see appendix C.4.2-6 for the search rationale). This search produced 320 unique hits. After screening of the title and the abstract based on our inclusion criteria, 292 articles were excluded. The complete article was screened for 28 articles; ultimately, the search yielded two additional studies, one RCT (Bellido-Fernandez 2018) and one systematic review (Kizhakkeveettil 2014). The studies included in the systematic review by Kizhakkeveettil were assessed based on the inclusion criteria of our clinical question. This did not yield any additional inclusions. The total number of analysed studies therefore amounts to two. See appendix C.4.2-1 for the flowchart of the inclusion process.
In line with the Cochrane review, we defined massage as 'soft-tissue manipulation applied manually or with a mechanical device'. Massage can be applied to any part of the body, only on the lumbar region or over the entire body. We used the taxonomy of massage treatments for musculoskeletal pain that was developed by Sherman in 2006 (Sherman 2006). The taxonomy was conceptualised as a classification system with three levels (treatment goals, styles and techniques) and four categories (relaxation massage, clinical massage, education about movement patterns and energy management). For the achievement of treatment goals, Sherman defined styles, with a set of techniques for each style. Of the 36 techniques in total, many can be incorporated in several styles (see appendix C.4.2-8 for the taxonomy used). When answering the clinical question about massage, we excluded the articles about techniques focused on energy pathways.

Characteristics of the included studies

The characteristics of the included studies are provided in appendix C.4.2-3. The search yielded two RCTs (Bellido-Fernandez 2018; Preyde 2000) and one systematic review (Kizhakkeveettil 2014). The two RCTs about exercise therapy and massage included a total of 131 patients with low back pain. The average age of the patients varied between 33 and 48 years, and the percentage of women was 49% to 85%. One study indicated the average duration of the complaints, specifically 12.5 weeks; in the other study the minimal duration of the complaints was 12 weeks. Neither study reported data about the percentage of patients with sciatica into the legs.

Individual study quality (RoB)

The design and execution of the individual studies (risk of bias, RoB) was assessed by NS with the help of the Cochrane Risk-of-Bias tool (Higgins 2011). An overview of the study quality assessment (RoB) per study is provided in appendix C.4.2-4.

Effectiveness and evidentiary value of exercise therapy and massage versus exercise therapy

The effect of exercise therapy and massage compared to exercise therapy alone is described in two RCTs (Bellido-Fernandez 2018; Preyde 2000). One RCT did not report any standard deviation, and it was not possible to calculate this based on other data (Bellido-Fernandez 2018). An overview of the results of the study by Preyde 2000 in the short term is depicted in the following table.
See appendix C.4.2-8 (figures 1 and 2) for the forest plots of the outcomes on pain and physical functioning in the short term.
No RCTs were found that measured the effect on pain and/or physical functioning in the long term.

GRADE evidence profile of the studies on exercise therapy and massage versus exercise therapy alone in the short term (≤4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Pain (VAS 0-100)										
1	severe[1]	not severe	not severe	severe[2]	not determined	25	22	MD 18.20 (10.03; 26.37)	low	crucial
Physical functioning (0-24)										
1	severe[1]	not severe	not severe	severe[2]	not determined	25	22	MD 4.17 (2.02; 6.3)	low	crucial
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RoB = risk of bias; RR = risk ratio; SF-36 = 36-Item Short Form Health Survey; VAS = Visual Analogue Scale.
[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 1 level due to a sample size <400.
Note: A higher score corresponds to less pain and a higher level of physical functioning. A positive MD represents an advantage for the intervention group.

Considerations

To answer the clinical question, other considerations were also included in the literature to recommendation process in addition to the literature. Together they determine the direction and strength of the recommendation. The assessment of considerations and the explanation are provided in appendix C.4.2-5.

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Note C.4.3 Transcutaneous electrical nerve stimulation (TENS) and interference

Literature

To answer the clinical question, a systematic literature analysis was carried out on the following research questions (PICO):

- What are the desirable and undesirable effects (O) of TENS and interference (I) versus no TENS or interference (C) in patients with low back pain with or without sciatica, without important warning signs (P)?
  We understand 'no TENS or interference' to mean: 1) doing nothing/waiting, 2) placebo/sham, 3) another intervention within the guideline (including information and advice, (pain) education, CGT).
- What are the desirable and undesirable effects (O) of TENS and interference as a supplement to exercise therapy (I) versus exercise therapy alone (C) in patients with low back pain with or without sciatica, without important warning signs (P)?

Based on the literature, the guideline panel selected 'pain' and 'physical functioning' as crucial outcome measures (Chiarotto 2015; ICHOM Working Group Members for Low Back Pain 2017; Verburg 2019). Undesirable effects are all negative effects that may be related to the intervention (e.g. increased pain and/or limitations in physical functioning, or pain and/or limitations in physical functioning of a type other than the kind for which one initially sought help, occurring immediately after the intervention).

Search

The literature review was conducted in a hierarchical manner; the search first focused on existing systematic reviews, possibly as part of an evidence-based guideline (see A.1 'Introduction'). Based on this search, a guideline of the National Institute for Health and Care Excellence (NICE) on the non-invasive treatments of low back pain and sciatica was identified (De Campos 2017). Because the NICE guideline is aimed at patients with the entire spectrum of back pain (from acute to chronic, with or without sciatica), and this is aligned with the delineation of our guideline (see section A.1 'Introduction'), in answering the clinical question about TENS we opted to use the NICE guideline as a basic principle and to implement an update of the search.

The NICE guideline is of high methodological quality (Lin 2018) and contains a clinical question of which TENS is a part, in accordance with that in our guideline: "What is the clinical and cost effectiveness of electrotherapy (non-invasive interventions) in the management of non-specific low back pain and sciatica?"
To answer this question, NICE searched in MEDLINE, Embase and the Cochrane Library up to 15 December 2015, after which 18 studies were included. These studies were tested according to our predefined inclusion criteria. See the following table.

Selection criteria for the search on literature about TENS and interference

Type of studies	randomised controlled study published in English or Dutch
Type of patients	adults with low back pain with or without sciatica, without important warning signs (see A.1 'Introduction') **Exclusion:** generalised chronic pain
Type of intervention	**PICO 1:** TENS or interference **PICO 2:** TENS or interference as a supplement to exercise therapy **Exclusion:** percutaneous electrical nerve stimulation, peripheral nerve stimulation, neuromuscular muscle stimulation
Type of comparison	**PICO 1:** do nothing/waiting/waitlist placebo/sham another intervention pursuant to the guideline (including information and advice, (pain) education, CGT). **PICO 2:** exercise therapy **Exclusion:** a different type of TENS or interference, intervention consisting of a simple application of TENS, a control group consisting of an invasive intervention (operations, epidural, facet blockade/injections) or pain medication
Type of outcome	At least one of the following outcome measures: **Desirable:** **Crucial:** pain, physical functioning **Undesirable:** all negative effects that might be related to the intervention
Type of timeline	Short (≤4 months) and/or long (>4 months) term. In the event of multiple measurement points, the measurement point that is closest to this time indication is used.

Nine of the 18 studies fulfilled the inclusion criteria and were analysed, of which two studies described the effectiveness of interference (Facci 2011; Hurley 2004) and seven studies were about TENS (Buchmuller 2012; Deyo 1990; Itoh 2009; Kofotolis 2008; Lehmann 1986; Marchand 1993; Topuz 2004). The articles that were excluded based on the complete text and the reason for the exclusion are listed in appendix C.4.3-2.
On 29 April 2020, an information specialist (J.W. Schoones, Leiden University Medical Centre) conducted a systematic search in PubMed, MEDLINE, Embase, Emcare, Web of Science and the Cochrane Library for updating of the NICE guideline (see appendix C.4.3-6 for the search rationale). The update of the systematic search of the NICE guideline produced 466 unique hits. After screening of the title and the abstract based on the inclusion criteria, 194 articles were excluded. The complete article was screened for 44 articles; ultimately, the search for updating the NICE guideline yielded eight additional studies, of which four were about interference and four about

TENS (Albornoz-Cabello 2017; Correa 2016; Elserty 2016; Franca 2019; Jamison 2019; Rajfur 2017; Tantawy 2020; Yurdakul 2019). The total number of studies in this literature analysis therefore amounts to 17. See appendix C.4.3-1 for the flowchart of the inclusion process.

Characteristics of the included studies

TENS

The characteristics of the included studies are provided in appendix C.4.3-3. The 11 included studies about TENS included a total of 652 patients with low back pain. The average age of the patients varied between 35 and 53 years, and the percentage of women varied from 31% to 100%. The average duration of the complaints was 1.5 to 13 years. Four studies did not report the duration of the complaints, but these studies also indicated that they included patients with chronic (> 3 months) low back pain. Four studies included a combination of patients with and without sciatica, whereby the percentage of patients with sciatica into the legs varied from 12% to 59% (Buchmuller 2012; Deyo 1990; Facci 2011). One study did not report any data about the percentage of patients with sciatica into the legs (Lehmann 1986). Four studies included patients without sciatica (Elserty 2016; Itoh 2009; Kofotolis 2008; Rajfur 2017) and in another four studies it was unknown whether there was sciatica into the legs (Jamison 2019; Marchand 1993; Topuz 2004; Yurdakul 2019). One study included only patients with sciatica into the legs (Franca 2019).

Interference

The characteristics of the six included RCTs are provided in appendix C.4.3-3. The studies included a total of 569 patients with low back pain, whose average age varied from 34.5 to 51.2 years, and the percentage of women was 57.5 to 83%. Five RCTs included patients with chronic (> 3 months) low back pain; in one RCT the average duration of the complaints was eight weeks (Hurley 2004). Two RCTs included both patients with and without sciatica, with the share of patients with sciatica into the legs being 24.6% in one RCT; this was not reported in the other RCT. One RCT included patients without sciatica, and in three RCTs it was unknown whether patients had sciatica into the legs.

Individual study quality (RoB)

The design and execution of the individual studies (risk of bias, RoB) was assessed by JMDM and NS with the help of the Cochrane Risk-of-Bias tool (Higgins 2011). The opinion of the various items was discussed, after which consensus was achieved. An overview of the study quality assessment (RoB) per study is provided in appendix C.4.3-4.

The effectiveness and evidentiary value of TENS versus doing noting/waiting/waitlist

The effectiveness and evidentiary value of TENS compared to doing noting/waiting/waitlist is described in four RCTs (Facci 2011; Itoh 2009; Marchand 1993; Yurdakul 2019). The results of one RCT could not be pooled because no standard deviation was reported, and it was not possible to calculate this based on other data (Marchand 1993).

An overview of the results in the short term that could be pooled is depicted in the following table. See appendix C.4.3-7 (figures 1 and 2) for the forest plots of the outcomes on pain and physical functioning in the short term.

GRADE evidence profile of the studies on TENS versus doing noting/waiting/waitlist in the short term (≤4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*) I	Patients (*n*) C	Effect size (95% CI)		
Pain (VAS 0-100)										
3	severe[1]	severe[2]	not severe	severe[3]	not determined	79	80	MD 23.16 (3.78; 50.10)	very low	crucial
Physical functioning										
3	severe[1]	not severe[2]	not severe	severe[3]	not determined	79	80	SMD 0.70 (0.04; 1.44)	very low	crucial
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RoB = risk of bias; RR = risk ratio; SF-36 = 36-Item Short Form Health Survey; VAS = Visual Analogue Scale.
[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 1 level due to unexplained heterogeneity. 3 Down-graded by 1 level due to a sample size <400.
Note: A higher score corresponds to less pain and a higher level of physical functioning. A positive MD represents an advantage for the intervention group.

No RCTs were found that measured the effect on pain and/or physical functioning in the long term.

Effectiveness and evidentiary value of TENS versus placebo/sham

The effect of TENS compared to placebo/sham is described in six RCTs (Buchmuller 2012; Deyo 1990; Kofotolis 2008; Lehmann 1986 Marchand 1993; Topuz 2004). The results of three RCTs could not be pooled because no standard deviation was reported, and it was not possible to calculate this based on other data (Buchmuller 2012; Lehmann 1986; Marchand 1993).
An overview of the results in the short term that could be pooled is depicted in the following table. See appendix C.4.3-7 (figures 3 and 4) for the forest plots of the outcomes on pain and physical functioning in the short term.

GRADE evidence profile of the studies on TENS versus doing noting/waiting/waitlist in the short term (≤4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*) I	Patients (*n*) C	Effect size (95% CI)		
Pain (VAS 0-100)										
2	severe[1]	severe[3]	not severe	severe[4]	not determined	103	98	MD 7.17 (2.78; 17.11)	very low	crucial

Physical functioning (ODI 0-100)										
2	very severe[2]	severe[3]	not severe	severe[4]	not determined	38	38	MD 2.21 (6.36; 10.78)	very low	crucial
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RoB = risk of bias; RR = risk ratio; SF-36 = 36-Item Short Form Health Survey; VAS = Visual Analogue Scale.
[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 2 levels because more than 50% of participants comes from studies with a selection and performance bias. [3] Down-graded by 1 level due to unexplained heterogeneity. [4] Down-graded by 1 level due to a sample size <400.
Note: A higher score corresponds to less pain and a higher level of physical functioning. A positive MD represents an advantage for the intervention group.

No RCTs were found that measured the effect on pain and/or physical functioning in the long term.

Effectiveness and evidentiary value of TENS versus another intervention within the guideline

The effect of TENS compared to another intervention within the guideline (in this case usual care or exercise therapy) is described in three RCTs (Franca 2019; Jamison 2019; Kofotolis 2008).
An overview of the results in the short term is depicted in the following table. See appendix C.4.3-7 (figures 5 and 6) for the forest plots of the outcomes on pain and physical functioning in the short term.

GRADE evidence profile of the studies on TENS versus another intervention within the guideline in the short term (≤4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Pain (VAS 0-100)										
3	severe[1]	severe[3]	not severe	severe[4]	not determined	72	74	MD 8.09 (29.11; 12.93)	very low	crucial
Physical functioning (ODI 0-100)										
2	very severe[2]	not severe	not severe	severe[4]	not determined	43	43	MD 14.28 (17.12; 11.44)	very low	crucial
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MCS = Mental Component Score; MD = mean difference; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; PCS = Physical Component Score; RCTs = randomized controlled trials; RoB = risk of bias; RR = risk ratio; SF-36 = 36-Item Short Form Health Survey; VAS = Visual Analogue Scale.

[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 2 levels because more than 50% of participants comes from studies with a selection and performance bias. [3] Down-graded by 1 level due to unexplained heterogeneity. 4 Down-graded by 1 level due to a sample size <400.
Note: A higher score corresponds to less pain and a higher level of physical functioning. A positive MD represents an advantage for the intervention group

No RCTs were found that measured the effect on pain and/or physical functioning in the long term. Franca's RCT is the only study within this literature review that included exclusively patients with low back pain with sciatica into the legs. Given that the heterogeneity of the results cannot be explained by this, no sensitivity analysis was conducted for patients with low back pain with sciatica into the legs.

Effectiveness and evidentiary value of TENS as a supplement to exercise therapy versus exercise therapy alone

The effect of TENS as a supplement to exercise therapy compared to exercise therapy alone is described in three RCTs (Elserty 2016; Kofotolis 2008; Rajfur 2017).
An overview of the results in the short term that could be pooled is depicted in the following table. See appendix C.4.3-7 (figures 7 and 8) for the forest plots of the outcomes on pain and physical functioning in the short term.
Note: All three RCTs included patients with low back pain without sciatica into the legs.

GRADE evidence profile of the studies on TENS as a supplement to exercise therapy versus exercise therapy alone in the short term (≤4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Pain (VAS 0-100)										
3	very severe[1]	severe[2]	not severe	severe[3]	not determined	73	59	MD 11.06 (6.45; 28.57)	very low	crucial
Physical functioning (ODI 0-100)										
3	very severe[1]	severe[2]	not severe	severe[3]	not determined	50	51	MD 1.44 (11.09; 13.98)	very low	crucial
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MD = mean difference; NPRS = Numeric Pain Rating Scale; N/A= not applicable; ODI = Oswestry Low Back Pain Disability Index; RCTs = randomized controlled trials; RR = risk ratio; RoB = risk of bias; VAS = Visual Analogue Scale.
[1] Down-graded by 2 levels because more than 50% of participants comes from studies with a selection and performance bias. [2] Down-graded by 1 level due to unexplained heterogeneity. [3] Down-graded by 1 level due to a sample size <400.
Note: A higher score corresponds to less pain and a higher level of physical functioning. A positive MD represents an advantage for the intervention group.

No RCTs were found that measured the effect on pain and/or physical functioning in the long term.

Effectiveness and evidentiary value of interference versus doing noting/waiting/waitlist

The effect of interference compared to doing noting/waiting/waitlist is described in one RCT (Facci 2011).

An overview of the results in the short term is depicted in the following table. See appendix C.4.3-7 (figures 9 and 10) for the forest plots of the outcomes on pain and physical functioning in the short term.

GRADE evidence profile of interference versus doing noting/waiting/waitlist (≤4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Pain (VAS 0-100)										
1	severe[1]	not severe	not severe	severe[2]	not determined	50	50	MD 44.10 (34.20; 54.00)	low	crucial
Physical functioning (RMDQ, 0-24)										
3	severe[1]	not severe	not severe	severe[3]	not determined	50	50	MD 7.51 (5.50; 9.52 hoger)	low	crucial
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MD = mean difference; N/A= not applicable; NPRS = Numeric Pain Rating Scale; ODI = Oswestry Low Back Pain Disability Index; RCTs = randomized controlled trials; RoB = risk of bias; RR = risk ratio; VAS = Visual Analogue Scale.

[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 1 level due to a sample size <400.

Note: A higher score corresponds to less pain and a higher level of physical functioning. A positive MD represents an advantage for the intervention group.

No RCTs were found that measured the effect on pain and/or physical functioning in the long term.

Effectiveness and evidentiary value of interference versus placebo/sham

The effect of interference compared to placebo/sham is described in two RCTs (Correa 2016; Tantawy 2020).

An overview of the results in the short term is depicted in the following table. See appendix C.4.3-7 (figures 11 and 12) for the forest plots of the outcomes on pain and physical functioning in the short term.

GRADE evidence profile of the studies on interference versus placebo/sham in the short term (≤4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*) I	Patients (*n*) C	Effect size (95% CI)		
Pain (VAS 0-100)										
2	severe[1]	severe[3]	not severe	very severe[5]	not determined	127	80	MD 11.66 (8.12; 31.43)	very low	crucial
Physical functioning (RMDQ, 0-24)										
1	very severe[2]	not severe	not severe	severe[4]	not determined	97	49	MD 1.15 (1.56; 3.86)	very low	crucial
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MD = mean difference; N/A= not applicable; NPRS = Numeric Pain Rating Scale; ODI = Oswestry Low Back Pain Disability Index; RCTs = randomized controlled trials; RoB = risk of bias; RR = risk ratio; VAS = Visual Analogue Scale.
[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 2 levels because more than 50% of participants comes from studies with a selection and performance bias. [3] Down-graded by 1 level due to unexplained heterogeneity. [4] Down-graded by 1 level due to a sample size <400. [5] Down-graded by 2 levels due to a very small sample size and the 95% CI (almost) exceeds a clinically relevant effect in favour of the control groups and a clinically relevant effect in favour of the intervention group (broad confidence interval).
Note: A higher score corresponds to less pain and a higher level of physical functioning. A positive MD represents an advantage for the intervention group.

No RCTs were found that measured the effect on pain and/or physical functioning in the long term.

Effectiveness and evidentiary value of interference versus another intervention within the guideline

The effect of interference compared to another intervention within the guideline is described in three RCTs (Albornoz-Cabello 2017; Hurley 2004; Rajfur 2017).
An overview of the results in the short term and the long term is depicted in the following tables. See appendix C.4.3-7 for the forest plots of the outcomes on pain and physical functioning in the short term (figures 13 and 14) and the long term (figures 15 and 16).

GRADE evidence profile of the studies on interference versus another intervention within the guideline in the short term (≤4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*) I	Patients (*n*) C	Effect size (95% CI)		
Pain (VAS 0-100)										
1	severe[1]	not severe	not severe	severe[2]	not determined	44	20	MD 15.50 (6.13; 24.87)	low	crucial

Physical functioning (RMDQ, 0-24)										
1	severe[1]	not severe	not severe	very severe[3]	not determined	44	20	MD 3.58 (4.56; 11.72)	very low	crucial
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MD = mean difference; N/A= not applicable; NPRS = Numeric Pain Rating Scale; ODI = Oswestry Low Back Pain Disability Index; RCTs = randomized controlled trials; RoB = risk of bias; RR = risk ratio; VAS = Visual Analogue Scale.
[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 1 level due to a sample size of <400. [3] Down-graded by 2 levels due to a very small sample size and the 95% CI (almost) exceeds a clinically relevant effect in favour of the control groups and a clinically relevant effect in favour of the intervention group (broad confidence interval).
Note: A higher score corresponds to less pain and a higher level of physical functioning. A positive MD represents an advantage for the intervention group.

GRADE evidence profile of the studies on interference versus another intervention within the guideline in the long term (> 4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Pain (VAS 0-100)										
1	severe[1]	not severe	not severe	very severe[4]	not determined	55	52	MD 8.30 (1.06; 17.66)	very low	crucial
Physical functioning (RMDQ, 0-24)										
1	very severe[2]	not severe	not severe	severe[3]	not determined	55	52	MD 1.85 (0.08; 3.62 higher)	very low	crucial
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MD = mean difference; N/A= not applicable; NPRS = Numeric Pain Rating Scale; RCTs = randomized controlled trials; RMDQ = 'Roland Morris Disability Questionnaire'; RoB = risk of bias; RR = risk ratio; VAS = Visual Analogue Scale.
[1] Down-graded by 1 level because more than 50% of participants comes from studies with a selection and/or performance bias. [2] Down-graded by 2 levels because more than 50% of participants comes from studies with a selection and performance bias. [3] Down-graded by 1 level due to a sample size of <400. 4 Down-graded by 2 levels due to a very small sample size and the 95% CI exceeds no effect and a small effect and a small effect in favour of the control group to a large effect in favour of the intervention group (broad confidence interval).
Note: A higher score corresponds to less pain and a higher level of physical functioning. A positive MD represents an advantage for the intervention group.

Effectiveness and evidentiary value of interference as a supplement to exercise therapy versus exercise therapy

The effect of interference as a supplement to exercise therapy versus exercise therapy is described in one RCT (Rajfur 2017). An overview of the results in the short term is depicted in the following table. See appendix C.4.3-7 (figures 17 and 18) for the forest plots of the outcomes on pain and physical functioning in the short term. No RCTs were found that measured the effect on pain and/or physical functioning in the long term.

GRADE evidence profile of the studies on interference as a supplement to exercise therapy versus exercise therapy (≤4 months)

RCT's (*n*)	Quality assessment (down-grading)					Summary of results			Evidentiary value	
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)		Effect size (95% CI)		
						I	C			
Pain (VAS 0-100)										
1	very severe[1]	not severe	not severe	severe[2]	not determined	21	21	MD 31.40 (28.16; 34.64)	very low	crucial
Physical functioning (ODI 0-100)										
1	very severe[1]	not severe	not severe	severe[2]	not determined	21	21	MD 27.92 (23.88; 31.96)	very low	crucial
Undesirable effects										
0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

95% CI = 95% confidence interval; C = control group; I = intervention group; MD = mean difference; N/A= not applicable; NPRS = Numeric Pain Rating Scale; RCTs = randomized controlled trials; ODI = Oswestry Low Back Pain Disability Index; RoB = risk of bias; RR = risk ratio; VAS = Visual Analogue Scale.

[1] Down-graded by 2 levels because more than 50% of participants comes from studies with a selection and performance bias. [2] Down-graded by 1 level due to a sample size <400.

Note: A higher score corresponds to less pain and a higher level of physical functioning. A positive MD represents an advantage for the intervention group.

Considerations

To answer the clinical question, other considerations were also included in the literature to recommendation process in addition to the literature. Together they determine the direction and strength of the recommendation. The assessment of considerations and the explanation are provided in appendix C.4.3-5.

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Note C.5 Completion of the treatment

Literature

See A.1 'Introduction' for information on the systematic search for evidence-based guidelines and systematic reviews.

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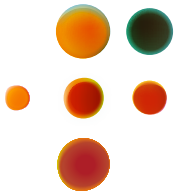
Colophon

Final editing: Tertius – Redactie en organisatie, Houten
Creative concept and design: C10 Ontwerp, The Hague

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 17,000 registered physical therapists.



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