Koninklijk Nederlands
Genootschap voor Fysiotherapie

Royal Dutch Society for Physical Therapy

Vereniging van Oefentherapeuten

## Justification

# *KNGF Guideline*
# on COPD

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## Explanation

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

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

| **Guideline panel** | |
|---|---|
| Prof. P.J. van der Wees | Chair of the guideline panel |
| J. Donkers | Patient, lung experience expert, Lung Foundation |
| J.K. de Jong, M.Eng | Patient, lung experience expert, Lung Foundation |
| Prof. D. Langer | Researcher, physical therapist |
| Prof. J.W.M. Muris | General practitioner, representative of the NHG-CAHAG |
| H. van der Niet-Colijn (until September 2019) | Nurse, representative of the V&VN |
| T.A.M. Peters-Ebbing | Exercise therapist C/M, representative of the VvOCM |
| S. van Riesen | Physical therapist in a secondary care setting, representative of the KNGF-NVZF |
| M.J. Schrasser, MSc | Senior policy advisor, Lung Foundation |
| M.J.H. Sillen, PhD | Physical therapist in a tertiary care setting, representative of the KNGF-VHVL |
| S. Simons, PhD | Pulmonologist, representative of the NVALT |
| N.M.C. Torrenga-Sieling, MSc (starting September 2019) | Nursing specialist in pulmonary medicine, representative of the V&VN |
| A. van der Valk, MSc | Physical therapist in a primary care setting, representative of the KNGF |
| M. Vooijs, MSc | Physical therapist in a tertiary care setting, representative of the KNGF |
| N.M. de Vries, PhD | Physical therapist (n.p.), researcher, representative of the KNGF-NVFG |
| C. Zagers, MSc | Physical therapist in a primary care setting, representative of the KNGF |

| **Review panel** | |
|---|---|
| Prof. P.J. van der Wees | Chair of the review panel |
| E. Bergkamp | Physical therapist in a secondary care setting, representative of the KNGF |
| E. van Biemen | Occupational therapist, representative of the EN |
| H. Bloo, MSc | Sports physical therapist in a primary care setting, representative of the KNGF-NVFS |
| M. Bregman | Physical therapist in a tertiary care setting, representative of the KNGF |
| G. Geraerts (starting April 2018) | Dietician, representative of the NVD |
| H. Horsman, MSc | Psychologist, representative of the NIP |
| A.J. van 't Hul, PhD | Researcher, physical therapist (n.p.) |
| F. IJpelaar | Paramedic advisor, representative of the ZN |
| S. van der Meer | Exercise therapist C/M, VvOCM |
| P. van Melick (until April 2018) | Dietician, representative of the NVD |
| H. Miedema, PhD | Medical advisor ZIN |
| C. Stevens (starting May 2019) | Paramedic advisor, representative of the ZN |
| L. Tissink, MSc | Physical therapist in a primary care setting, representative of the KNGF |

| **Authors** | |
|---|---|
| H.L. Vreeken, MSc (until July 2019) | Project manager, KNGF policy adviser |
| E. Beekman, PhD | Researcher (lecturer), instructor, physical therapist |
| M.C.M. van Doormaal, MSc (starting July 2019) | Project manager, KNGF policy adviser |
| M.H.T. Post, MSc | VvOCM policy adviser |
| G.A. Meerhoff | KNGF quality policy manager |
| Prof M.A. Spruit | Researcher, physical therapist, not practicing |

CAHAG = COPD & Astma Huisartsen Advies Groep (COPD and Asthma General Practitioners Advisory Panel); EN = Ergotherapie Nederland (Dutch Association of Occupational Therapists); KNGF = Koninklijk Nederlands Genootschap voor Fysiotherapie (Royal Dutch Society for Physical Therapy); NHG = Nederlands Huisartsen Genootschap (Dutch Society of General Practitioners); NVALT = Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (Dutch Association of Physicians in Chest Medicine and Tuberculosis); NIP = Nederlands Instituut van Psychologen (Dutch Institute of Psychologists); NVD = Nederlandse Vereniging van Diëtisten (Dutch Society of Dieticians); NVFG = Nederlandse Vereniging voor Fysiotherapie in de Geriatrie (Dutch Association for Physical Therapy in Geriatrics); NVZF = Nederlandse Vereniging voor Ziekenhuis Fysiotherapie (Dutch Society for Hospital Physical Therapy); VHVL = Vereniging voor Hart-, Vaat- en Longfysiotherapie (Association of Cardiovascular and Pulmonary Rehabilitation); NVFS = Nederlandse Vereniging voor Fysiotherapie in de Sportgezondheidszorg (Dutch Society for Physical Therapy in Sports Medicine); V&VN = Verpleegkundigen & Verzorgenden Nederland (Dutch Organisation for Nurses and Carers); VvOCM = Vereniging van Oefentherapeuten Cesar en Mensendieck (Association of Exercise Therapists Cesar and Mensendieck); ZIN = Zorginstituut Nederland (Healthcare Institute of the Netherlands); ZN = Zorgverzekeraars Nederland (Dutch Healthcare Insurance Companies). n.p. = not practising.

# Contents

## Justification

## Appendices

# A General information

## 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 was established pursuant to the AQUA guideline, GRADE, the AGREE II instrument and the Assessment Framework for Quality Standards (AGREE Next Steps Consortium 2010; AQUA 2014; GRADE Working Group 2008; ZiN 2018). The experts involved (Emmylou Beekman, phD, Prof Martijn Spruit and the KNGF) evaluate on a yearly basis whether contextual and/or policy developments necessitate a revision of the guideline.

### Preparation phase

A guideline panel and a review panel were set up containing representation from the following relevant parties:

| Guideline panel | Review panel |
|---|---|
| physical therapists: KNGF (including VHVL, NVFG, NVZF) | physical therapists: KNGF (including NVFS) |
| exercise therapists Cesar/Mensendieck (C/M): VvOCM | exercise therapists C/M: VvOCM |
| general practitioners: NHG-CAHAG | occupational therapists: EN |
| pulmonologists: NVALT | dieticians: NVD |
| nurses: V&VN | psychologists: NIP |
| | ZiN |

CAHAG: COPD & Astma Huisartsen Advies Groep (COPD and Asthma General Practitioners Advisory Panel); KNGF: Koninklijk Nederlands Genootschap voor Fysiotherapie (Royal Dutch Society for Physical Therapy); NHG: Nederlands Huisartsen Genootschap (Dutch College of General Practitioners); NIP: Nederlands Institute van Psychologists (Dutch Institutesociation of Cardiovascular and Pulmonary Rehabilitation); V&VN: Verpleegkundigen & Verzorgenden Nederland (Dutch Organisation for Nurses and Carers); VvOCM: Vereniging van Oefentherapeuten Cesar en Mensendieck (Association of Cesar and Mensendieck Exercise Therapists); ZN: zorgverzekeraars Nederland (Dutch Healthcare Insurance Companies); ZiN: Zorginstituut Nederland (Healthcare Institute of the Netherlands)

All involved guideline panel and review panel members signed a conflicts of interest statement at the start of the project. Four review focus groups convened in the preparation phase (two with therapists and two with patients) during which the barriers were assessed. A total of 22 therapists and 12 patients (and one caregiver) took part in these focus groups. These barriers were subsequently presented to the members of the guideline panel and review panel during the first guideline panel meeting or review panel meeting, respectively. Several additional barriers were identified during this meeting. All barriers collected in this manner were subsequently converted into clinical questions.

### *Development phase*

For each clinical question, it was then determined how this question could best be answered: through a systematic review or by means of a narrative elaboration. If a systematic review was not indicated because such an approach would not be able to answer the question, subject-matter expert scientists reviewed literature in a narrative manner. For the clinical questions for which a systematic review was indicated, PICOs were compiled and – with the assistance of a librarian from the Leiden University Medical Centre (LUMC) – 'search-strings' were formulated that were used to search in the following databases: PubMed, EMBASE, Web of Science, Cochrane Library, CENTRAL, EmCare and CINAHL. Where possible, the search strings were combined for various clinical questions. Using pre-defined inclusion and exclusion criteria, the search results were selected based on – successively – title and abstract and then on the complete text. A KNGF guideline expert then compiled literature conclusions based on the included studies (size of the effect and reliability of the evidence)

as described in the 2019 KNGF Guideline Methodology (KNGF 2019). If an existing systematic review was used, and this was done where possible, then the assessment of the respective review was incorporated, with recent studies that appeared after the systematic review being added to the review. After the strength of the evidence and size of the effect were determined, sub-groups of guideline panel and review panel members formulated the remaining considerations, which were then discussed in seven meetings with the guideline panel and five meetings with the review panel based on the evidence-to-decision form (translated to Dutch) until consensus was achieved about the form. Based on the scientific evidence and the other considerations, the formulation (direction and strength) of the recommendation was determined. See the table.

*Formulation of recommendations*

| **Type of recommendation** | **Example of the formulation** |
|---|---|
| strong recommendation for the intervention | offer the intervention |
| conditional recommendation for the intervention | consider offering the intervention if.... |
| conditional recommendation against the intervention | preferably do not offer the intervention unless... |
| strong recommendation against the intervention | do not offer the intervention |

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. All recommendations, including the explanation and justification, together comprise the draft guideline.

### *Review and authorisation phase*

The draft guideline was then sent to all organisations that were represented in the guideline panel and/or review panel. In addition, several dozen physical and exercise therapists received the draft guideline for them to review. Where possible, all comments were processed by the authors and presented in writing to the guideline panel and review panel, after which another meeting of both the guideline panel and the review panel took place during which the last points of discussion were addressed. After being documented by the guideline panel and the review panel, the guideline was presented to all involved parties for authorisation.

### *Dissemination and implementation phase*

The following activities were/are being undertaken to promote implementation of the guideline:

- physical, nation-wide seminars;
- development of an e-learning module;
- publication of articles in magazines (both within and outside the fields of physiotherapy/exercise therapy both nationally and internationally);
- lectures at congresses and symposia;
- development of patient information.

Implementation activities are in particular aimed at the following five topics, which are also classified as key recommendations:

- difference between the treatable traits physical activity, physical capacity and respiratory system;
- patient profiles;
- reference for maximal exercise test;
- frequency, intensity, type and duration of physical training (FITT principles);
- treatment of specific sub-groups (co-morbidity, exacerbation and palliative phase).

### *Involvement of interested parties*

**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 draft guideline in the review phase and provided feedback on the implementation products, such as the e-learning, during the implementation phase.

**Patients**

In order to guarantee the patient perspective to the greatest extent possible, patients were already involved in the guideline development during the preparation phase. A total of 12 patients and one caregiver, dispersed across two focus groups, contributed barriers using a semi-structured method. The barriers, along with the barriers flagged by the therapists and the guideline panel and review panel, served as the basis for the clinical questions. Longfonds (Lung Foundation) representatives also took part in the development process, as part of the guideline panel and during the review phase. In addition, this patient association also contributed to development of the patient information.

**Other interested parties**

Other interested parties sat on the guideline panel or review panel and/or were involved in the guideline during the review phase and contributed to the creation of the guideline in this way.

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## Note A.2 COPD background

### Note A.2.1 Pathophysiology

#### Clinical question

**What is the pathophysiology of COPD?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

#### References

GOLD. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Fontana, CA, USA: Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2020.

### Note A.2.2 Clinical presentation

#### Clinical question

**How can the therapist best set goals together with the patient?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

#### References

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### Note A.2.3 Etiological and prognostic factors

#### Clinical question

**What are the etiological and prognostic factors of COPD?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

#### References

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### Note A.2.4 Epidemiology and societal impact

#### Clinical questions

**What are the epidemiology and societal impact of COPD?**

1. **What is de prevalence and incidence of COPD (epidemiology)?**
2. **What is the societal impact of COPD?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

#### References

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## Note A.3 Organisation of care

### Note A.3.1 The therapist's role

#### Clinical question

**What is the role of the therapist in the healthcare process of COPD patients?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

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### Note A.3.2 Organisation of multidisciplinary collaboration

#### Clinical question

**How is multidisciplinary collaboration organised for COPD patients?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

#### References

LAN. COPD Healthcare Standard. Amersfoort: Longalliantie Nederland (LAN) (Dutch Lung Alliance); 2016.

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NHG. NHG COPD Standard. Utrecht: Nederlands Huisartsen Genootschap (NHG) (Dutch College of General Practitioners); 2015.

### Note A.3.3 Treatable traits for physiotherapy and exercise therapy C/M

#### Clinical question

**What are the most important treatable traits for physiotherapy and exercise therapy C/M for COPD patients?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

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### Note A.3.4 Information exchange with referring physicians

#### Clinical questions

1. **Which information does the therapist need from the referring physician (general practitioner or pulmonologist)?**
2. **Which information does the therapist report to the referring physician?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

#### References

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## B Diagnostic process

### Note B.1 Medical history taking

#### Clinical question

**Which information is collected when taking the medical history of a COPD patient?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

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## Note B.2 Physical examination

### Clinical question

**What does the physical examination for a COPD patient consist of?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

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## Noot B.3 Meetinstrumenten

### Noot B.3.1 Aanbevolen en optionele meetinstrumenten

### Clinical questions

- **Which parameters are objectified per ICF domain with the help of measurement instruments for diagnostic, prognostic and/or evaluation purposes?**
- **Which measurement instruments best assess the parameters per ICF domain per objective (recommended and optional measurement instruments)?**

The action plan of the Raamwerk Klinimetrie (Clinimetric Framework) was employed when selecting the measurement instruments (KNGF 2016a, KNGF 2016b).

The action plan consists of the following eight steps:
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 and 8 – Are standard values available and how do you calculate and interpret the data?

The choice of measurement instrument is justified for each step, after which the recommended and optional measurement instrument are differentiated.

**Step 1 – What do you want to measure?**
This guideline lists the parameters that therapists can assess during the diagnostic and therapeutic process in COPD patients in relation to the patient's need for assistance.
The following relevant parameters were formulated, sub-divided by ICF domain:

- Functions and anatomical characteristics: physical capacity/exercise capacity (functional and maxi mal), oxygen saturation, dyspnoea, fatigue, muscle strength, respiratory muscle function, pain, balance
- Activities and participation: physical activity, activities and participation during ADL risk of falling
- External factors: none
- Personal factors: symptom burden, nutritional status, anxiety and/or depression

These parameters can be assessed during the medical history taking, the physical exam, the screening for red flags, for the purposes of a possible referral, setting goals, monitoring during the exercise therapy and for the purposes of the (final) evaluation.

**Step 2 – Why do you want to measure?**
All of the parameters listed in step 1 can be measured with both a diagnostic goal as well as an evaluative goal. There are no parameters that are measured explicitly with a prognostic goal.

**Step 3 – What kind of measurement instrument do you want to use to measure?**
For each parameter, a narrative search was conducted for measurement instruments that are suitable for assessing the parameter. Parameters that correspond were combined, after which a search was conducted for a measurement instrument that can assess both parameters.

*Physical capacity/exercise capacity*
The exercise capacity can be assessed as functional and as maximal exercise capacity. For assessing the functional exercise capacity, an analysis was conducted of the Six Minute Walk Test (6MWT) and variations thereof, the Two Minute Walk Test (2MWT), The Twelve Minute Walk Test (12MWT), the Shuttle Walk Test (SWT), the Incremental Shuttle Walk Test (ISWT), the Endurance Shuttle Walk Test (ESWT) and the Constant Work Rate cycle Test (CWRT). For assessing the maximal exercise capacity, the Cardiopulmonary Exercise Test (CPET) was analysed.

*Oxygen saturation*
The oxygen saturation (Sp02) is measured in order to decide, based on the outcome of this measurement, whether or not to start the physical training. The Sp02 can also be used to determine whether it is necessary to adapt the intensity during the exercise or stop the exercise and refer the patient back, if needed. The Sp02 is also measured to determine saturation recovery after exercise.
A saturation meter is used to conduct the transcutaneous non-invasive measurement of the Sp02 using a finger, earlobe or forehead (Garvey 2016).

*Dyspnoea*
To assess dyspnoea, the Borg Dyspnoea Scale, the Medical Research Council Dyspnoea Scale (MRC) and the modified Medical Research Council Dyspnoea Scale (mMRC) were analysed.

*Fatigue*
To assess fatigue, the Borg Fatigue Scale, the Visual Analogue Scale (VAS) for Fatigue and the Checklist Individual Strength (CIS) were analysed.

*Muscle strength*
To assess muscle strength, the Hand-Held Dynamometer (HHD), the Isokinetic Dynamometer, the One-Repetition maximum test (1RM) and the 1RM submaximal test were analysed.

*Nutritional status*
To screen for possible malnutrition, the Malnutrition Universal Screening Tool (MUST) was analysed. For screening for sarcopenia, the SARC-F was analysed.

*Respiratory muscle function*
To assess the respiratory muscle function, the Maximal Inspiratory Pressure (MIP) was analysed.

*Pain*
To assess pain, the Numeric Pain Rating Scale (NPRS), the Visual Analogue Scale (VAS) and the Verbal Rating Scale (VRS) were analysed.

*Balance and risk of falling*
To assess the balance and risk of falling, an analysis was conducted of the Performance Oriented Mobility Assessment (POMA), the Functional Reach Test (FRT), the Get Up & Go test (GUG), the Timed Up & Go test (TUG), the Berg Balance Scale (BBS) and the Standing on One Leg rapid test.

*Physical activity*
To assess physical activity, both questionnaires as well as activity meters were analysed.

*Activities and participation in ADL*
To assess activities and participation in ADL, the Patient-Specific Complaints (PSC) and the Patient Specific Goal-setting method (PSG) were analysed.

*Symptom burden*
To assess the symptom burden, an analysis was conducted of the Quality of Life for Respiratory Illness Questionnaire (QoLRIQ), the Chronic Respiratory (Disease) Questionnaire (CR(D)Q), the Short Form Chronic Respiratory Questionnaire ((SF)CRQ), the St. George's Respiratory Questionnaire (SGRQ), the St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C), the Clinical COPD Questionnaire (CCQ), the COPD Assessment Test (CAT) and the Respiratory Illness Questionnaire-Monitoring 10 (RIQ-MON10).

*Anxiety and depression*
To assess anxiety and depression, the Hospital Anxiety and Depression Scale (HADS) was analysed.

**Step 4 – How can you find a measurement instrument?**
All of the measurement instruments listed in this guideline are available or can be made available at www.meetinstrumentenzorg.nl.

**Step 5 – What is the practicability?**

*Physical capacity/exercise capacity*
The duration of the 12MWT is greater than that of the 6MWT, the SWT and the 2MINWT, and the test is also more burdensome for the patient. The 6MWT is a simple test that can be used in various populations that cannot be tested with tests of longer duration (e.g. the 12MWT) or a test whereby an external tempo must be adhered to when walking (e.g. the SWT) (ERS/ATS 2014a; ERS/ATS 2014b). The 6MWT is a self-paced test and is commonly used in daily practice in the Netherlands. The test is considered to be very practical.
The SWT is often preferred in patients who have an inherently faster walking speed. The ISWT variation is very close to a patient's maximal exercise capacity (ERS/ATS 2014b). With the ESWT, the functional exercise capacity is measured. For the ESWT, which just like the ISWT is not self-paced, the ISWT must first be performed twice (ERS/ATS 2014a; ERS/ATS 2014b). Both tests are considered to be sufficiently practical.
With the CWRT, the duration of the test depends on the patient's persistence time at a constant workload of 75% of the previously determined maximal cycle load (Van 't Hul 2003) and doesn't last more than 15-20 minutes on average for healthy adults (Neder 2000). Although a measurement of the CPET is necessary for performing the CWRT, the CWRT is considered to be sufficiently practical.
It is preferable for the CPET to be performed under the supervision of a pulmonologist, which requires a referral from the general practitioner. This test is considered to be sufficiently practical.

*Oxygen saturation*
The transcutaneous Sp02 can be measured easily and quickly in practice using the finger or earlobe. An oxygen saturation meter must be acquired, but the costs of this are low. The oxygen saturation meter is considered to be very practical due to this.

*Dyspnoea*
A modified version of the Borg Scale (0-10) has been developed for COPD that is similar to the Borg Rating of Perceived Exertion Scale (Borg RPE Scale, 6-20) (Borg 1982). This is a simple and short scale that is used very often by therapists in the Netherlands. The Borg Scale is considered to be very practical.
The mMRC is a practical scale with a short test time (< 1 min) that healthcare professionals or patients can complete themselves (Fletcher 1965; Cazzola 2015). However, general practitioners use the MRC instead of the mMRC (LAN 2016, NHG 2015). The MRC is also used by certain regional transmural networks in order to determine the setting in which the patient should be treated (HUS 2016). Given that the MRC score is simple to convert to an mMRC score, the mMRC is considered to be very practical.

*Fatigue*
There are many questionnaires for assessing fatigue (Hewlett 2011). The 'Fatigue' VAS is the most commonly used instrument at the international level (Hewlett 2011), but this instrument isn't comprehensive enough and is therefore insufficiently practical according to the guideline panel.
The Borg Scale is a simple and very practical instrument that can be applied during exercise tests (before and after the treatment) and during treatment. The scale is used frequently in the Netherlands (Borg 1982).
The Checklist Individual Strength (CIS) measures related subjective fatigue and behavioural aspects

with the help of 20 items that are distributed across four sub-scales (Vercoulen 1994, 1999). The test time is 4 to 10 minutes. Because using the entire CIS20R scale is burdensome for the patient, often only the 'Fatigue' sub-scale that contains eight items (CIS8R) is used (Goertz 2019; Hewlett 2011). Using the CIS8R sub-scale is considered to be very practical.

***Muscle strength***

Measuring large muscle groups is important for assessing peripheral muscle strength in COPD patients (Robles 2011). The HDD does not take much time to measure. In daily practice, the HHD is a portable, small instrument that is easy to use for a quick measurement. The instrument is relatively inexpensive (compared to isokinetic dynamometers, which are considered to be the golden standard but which require special knowledge, skill and equipment) (Schrama 2014). No HHD measurement of the upper extremity (e.g. shoulder abduction) is recommended; this is considered to be less relevant than measurement of the lower extremity. The HDD is considered to be sufficiently practical.

The 1RM maximum test also has a short test time. No additional equipment needs to be acquired for the measurement if the therapist already has strength equipment with precision settings. Doing the 1RM appears to be safe (Kaelin 1999). In contrast to the HHD, the 1RM cannot be used for diagnostic purposes. The 1RM can be used to help determine the training intensity for training on the same strength equipment as is used to conduct the measurement (Morree 2006). The 1RM is considered to be sufficiently practical.

***Nutritional status***

The MUST can identify (a risk of) malnutrition and the SARC-F can identify (the risk of) sarcopenia (Stuurgroep Ondervoeding [Malnutrition Steering Committee] 2015; Stuurgroep Ondervoeding [Malnutrition Steering Committee] 2019).

***Respiratory muscle function***

Acquisition of threshold equipment is necessary for an MIP measurement. A measurement is reliable if three repetitions differ from each other by less than 10%. A statement by the European Respiratory Society (ERS) contains more details about testing the respiratory muscle strength (ERS 2019a). If the threshold equipment is already available at the practice, this measurement instrument is considered to be practical.

***Pain***

Doing the NPRS, the VAS and the VRS takes about one minute. A systematic review shows that the NPRS has preference over the VAS and the VRS based on ease of use and applicability (Hjermstad 2011). Although all instruments are practical, the NPRS is considered to be the most practical.

***Balance and risk of falling***

The POMA (Tinetti test) is extensive and therefore takes 10 to 15 minutes (Tinetti 1986). This test is considered to be practical but takes a relatively long time and is more burdensome for patients than other measurement instruments.

The FRT is not very burdensome for patients (Duncan 1990), but it is one activity performed in one position and is therefore considered to be less practical than other measurement instruments.

The TUG is practical and simple to perform and should be performed twice (Mesquita 2013). The TUG is a modified version (with the added element of time) of the Get Up & Go test (GUG) and is also called the Timed Get Up & Go test (TGUG) (Barry 2014; Mathias 1986). The measurement instrument is ADL-specific and can also be used to measure functional exercise capacity if other exercise tests are not possible, for example in the home environment (Mesquita 2013). The TUG also provides insight into the 'standing up from a chair' and 'walking' activities. The TUG is considered to be very practical.

The 'standing on one leg' rapid test does not have a validated cut-off point on which to be able to base an increased risk of falling, and research on the BBS shows that the limit of 45 seconds is not suitable for detecting risk of falling (Muir 2008). As a result, both measurement instruments are considered to be not very practical.

***Physical activity***

Completing questionnaires that provide a global impression of physical activity in patients takes a long time, making this questionnaire not sufficiently practical.

The practicability of the currently commercially available activity meters varies. Patients do see the added value of using an activity meter for obtaining insight into their own exercise behaviour and to become motivated to exercise more, but this only applies if the meter provides feedback about the number of steps and potentially the number of active minutes (Ummels 2019). However, patients with chronic diseases (including COPD) find such activity meters to be technically complicated. They want the therapist's help when the meter is used

for the diagnostic and/or therapeutic process and do not want to spend too much money for it (at most 50) (Ummels 2019). The recommendation is to use activity meters that measure activities (i.e. exercise) in direct outcome measures, such as steps and active minutes (Van Remoortel 2012a).

*Activities and participation in ADL*
The PSG is the updated version of the PSC. The PSG can be used as a measurement instrument but simultaneously as a method to set goals together with the patient (Stevens 2013, 2017a). With the PSG, the PSC is taken immediately, due to which setting goals is more integrated into the therapeutic methodology (Stevens 2017b). The only thing you need is the – freely available – questionnaire and a pen. Depending on the target group and the time it takes to select activities, it takes an average of 5 to 15 minutes to take the PSG (Beurskens 1996). Because the PSG is part of the methodology, taking it does not require additional time (Stevens 2017a) and is therefore very practical. See also Note B.6 'Setting goals'.

*Symptom burden*
The most comprehensive disease-specific questionnaires, the QoLRIQ, the CRQ (and SF-CRQ) and the SGRQ (and SGRQ-C), are complex in use in daily practice. The CCQ and the CAT are more suitable in that situation (Cazzola 2015; GOLD 2020; Ringbaek 2012).
The 10-item CCQ and the 8-item CAT are simple questionnaires that can be completed by the patient (Van der Molen 2003; Jones 2009a). The average time to take the CAT is 107 seconds and the CCQ 134 seconds (Ringbaek 2012). Another suitable test is the RIQMON10, which has retained the good clinimetric properties of the original instrument, the QoLRIQ, and with 10 items (3 minutes to take) is very suitable for use in daily healthcare practice (Jacobs 2004). Both the CCQ and the RIQ-MON10 are listed in the COPD guideline for general practitioners (NHG 2015). The CCQ is used the most intensively by general practitioners in the Dutch therapeutic setting, while pulmonologists often use the CAT (LAN 2016). The CCQ, CAT and RIQMON10 are considered the most practical measurement instruments for determining the symptom burden.

*Anxiety and depression*
The HADS can be used to measure depression and anxiety in both a hospital setting as well as in daily practice for various target groups (Zigmond 1983). The questionnaire consists of 14 items that are divided equally over the sub-scales 'Anxiety' (HADS-A) and 'Depression' (HADS-D). The HADS does not adequately detect the presence of specific anxiety or depressive disorders and is not a medical diagnostic tool or a good predictor of specific diagnoses but does provide indications for generalised symptoms of anxiety and depression (Julian 2011). The HADS is easy to use. It's a short questionnaire that takes about 2 to 5 minutes to complete. The HADS is an often used questionnaire for quickly and easily assessing psychological symptoms and is considered to be very practical.

**Step 6 – What is the clinimetric quality?**

*Physical capacity/exercise capacity*
The 6MWT, SWT (including the ISWT and ESWT variations) and the CWRT all appear to be suitable for measuring the exercise capacity and are valid, reliable and responsive measurement instruments (ERS/ATS 2014a; ERS/ATS 2014b; GOLD 2020; O'Donnell 2009, Puente-Maestu 2016, Van 't Hul 2003).
The CPET is the only instrument that is suitable for measuring the maximal exercise capacity and is also considered to be the gold standard for this (ERS 2019a). The test reliability of the CPET for measuring the V02 max in people with COPD is good. The clinimetric quality of the 6MWT, ISWT/ESWT, CWRT and CPET is considered to be good.

*Oxygen saturation*
At about 4%, the precision of the oxygen saturation (Amalakanti 2016) is sufficient for detecting a significant decrease in oxygen saturation. Although there are signs that the measurement in COPD patients overestimates the Sp02 value (Amalakanti 2016), the finger saturation meter is accepted as a reliable instrument (Hess 2016; Nitzan 2014).
The measurement can be unreliable with an abnormal haemoglobin content, during exercise and when wearing nail polish or when the finger is cold (decreased peripheral circulation) (Hess 2016; Nitzan 2014). In this case, the measurement can be repeated somewhere else on the body, such as using the earlobe or using an adhesive sensor on the forehead (EN 2016). There are also practical considerations when choosing a specific measurement location. Measuring on the forehead appears to be closer to the arterial oxygen saturation (Sa02) than using the finger, but both sensors detect exercise-related desaturation (Wilson 2013). The clinimetric quality of the saturation meter is considered to be sufficient.

***Dyspnoea***
The 'Dyspnoea' Borg Scale was not examined for clinimetric properties, but the original Borg RPE scale is valid and correlates with the heart rate (Chen 2002; Colberg 2003; Penko 2017; Scherr 2013). The responsiveness in healthy adults is good (Buckley 2000). The mMRC correlates well with other measurements of the health status (Bestall 1999; Spruit 2007) and predicts the risk of mortality (Nishimura 2002; Sundh 2012a). A disadvantage of the mMRC is the low responsiveness (Cazzola 2015). The clinimetric quality both the 'Dyspnoea' Borg Scale and the mMRC is considered to be sufficient.

***Fatigue***
The 'Fatigue' Borg Scale is valid and correlates well with heart rate (Chen 2002; Colberg 2003; Penko 2017; Scherr 2013). The validity, reliability and responsiveness of the CIS8R (and of the CIS20R) are good, but these are primarily intensively tested in populations with rheumatoid arthritis (Hewlett 2011; Van Hoogmoed 2010; Van Hoogmoed 2008; Van Koulil 2009; Zijlstra 2007). In studies with COPD patients, the CIS is used as an outcome measure (Goërtz 2018, 2019). The clinimetric quality of the 'Fatigue' Borg Scale and of the CIS8R is considered to be sufficient.

***Muscle strength***
The validity, including the differentiation between the low and high muscle strength of the 1RM and of the sub-maximal version thereof is lower than that of the more objective methods, such as the (Schrama 2014). The HHD appears to be valid from a systematic review (Stark 2011). When measuring the quadriceps strength, the test-retest reliability of the HHD in COPD patients with severe to very severe airflow limitation was high (ICC 0.97) (Nyberg 2018). The reliability of the HDD (only the inter-rater reliability) for measuring the upper extremity was good (Schrama 2014). The clinimetric quality of both instruments is considered to be sufficient.

***Nutritional status***
Clinimetric properties of both the MUST and the SARC-F are considered to be sufficient (Malnutrition Steering Committee 2015; Malnutrition Steering Committee 2019).

***Respiratory muscle function***
The MIP measurement is suitable for determining and evaluating the maximal inspiratory muscle strength (Basso-Vanelli 2018; ERS 2019a). The measurement is reliable in COPD patients when multiple measurements are taken and the measurement is done by an experienced healthcare professional. The reliability can be negatively influenced in the presence of hyperinflation and/or a severe obstruction. The clinimetric properties of the MIP measurement are considered to be sufficient due to this.

***Pain***
The NPRS is sufficiently valid and responsive compared to the other pain scales (Ferreira-Valente 2011). Although the reproducibility of the total scores is sufficient, the NPRS does not score well in individual scores due to a large degree of variability (Van Tubergen 2002). The NPRS is preferred to the Visual Analogue Scale (VAS) based on good sensitivity (Williamson 2005). A systematic review shows that the NPRS has preference over the VAS and the VRS based on compliance and responsiveness (Hjermstad 2011). Based on this, the clinimetric properties of the NPRS are considered to be good.

***Balance and risk of falling***
The POMA has a better reliability and validity and can discriminate better than the FRT and the TUG, but all measurement instruments score low on responsiveness (Lin 2004). However, the TUG is sufficiently valid and responsive for COPD patients, has a good test-retest reliability and can also discriminate well (Al Haddad 2016; Mesquita 2013, 2016). The clinimetric qualities of the TUG is considered to be sufficient based on this.

***Physical activity***
The clinimetric quality of questionnaires is insufficient to obtain insight into the exercise behaviour of patients. Completing questionnaires or diaries result in an over-estimate of most activities, while low-intensive activities are underestimated due to this (Ainsworth 2015; Helmerhorst 2012). There is still insufficient research on the clinimetric quality of applications on smartphones, such as activity meters. Studies in which applications were also examined show that the validity of such applications varies among COPD patients, among others (Ummels 2018). More and more research is being done on activity meters, but of the studies on commercially available activity meters (without licensing costs and with limited acquisition costs per meter), only one single study has sufficient methodological quality. The validity of commercially available activity meters for counting the number of steps and the physical activity is good, but the validity of activity meters that measure

energy consumption and sleep is bad. However, these meters have often been studied in a healthy (athletic) adult population (Evenson 2015; Kooiman 2015; Van Remoortel 2012b). Additionally, the meters perform better at moderate and fast walking speeds than at lower walking speeds (Fokkema 2017). The clinimetric properties of activity meters appear to vary, but according to the guideline panel they are sufficient for including activity meters as a measurement instrument in this guideline.

*Activities and participation in ADL*
The methodological quality of the PSC was deemed to be good but was investigated for diseases other than COPD (Van der Wees 2012). The validity and responsiveness of the questionnaire are sufficient (Beurskens 1996; Rollman 2010; Van der Wees 2012). The reliability differs, depending on the selected activity (Nijkrake 2009). If VAS is used instead of the NRS for the questionnaire, the reliability of the PSC is sufficient (Rollman 2010). More research was done on the English version (Patient Specific Functional Scale) (PSFS). A review shows that the PSFS is valid, reliable and responsible (Barten 2012). Based on the clinimetric properties of the PSC, the clinimetric quality of the is also considered to be sufficient.

*Symptom burden*
Generic questionnaires, such as the EQ-5D and RIQMON10, are generally valid at the group level, but there are problems when using it for individual outcomes and in the presence of a bad response; this applies primarily for the RIQMON10, which is dropped due to this (Finch 2018). The CCQ is valid, reliable and responsive (also for evaluating interventions) (Ställberg 2009; Sundh 2012). The questionnaire has highly discriminating properties for all patients with COPD and for patients with a risk of COPD (Van der Molen 2003). The CCQ has been validated for use at the group level and or use at the individual level (Kocks 2006; Van der Molen 2003). The CAT is reliable and sensitive to changes in health status (after an exacerbation and during an intervention) (Dodd 2011, 2012; Smid 2017; Jones 2009b). The CCQ and CAT are considered to be the measurement instruments with the best clinimetric quality.

*Anxiety and depression*
Both the internal consistency of the sub-scales as well as the test-test reliability of the HADS is high (Bjelland 2002; Roberts 2001; Smarr 2011). Compared to other often used (but longer) questionnaires for assessing depression and anxiety (such as the Beck Depression Inventory and the General Health Questionnaire), the validity is good to very good (Julian 2011; Bjelland 2002; Smarr 2011). The discriminatory power of the HADS is moderate to high and comparable to other screening questionnaires (Bjelland 2002; Brennan 2010). The responsiveness of the HADS is good, especially in patients with high scores at the start of the intervention (Harrison 2012; Smid 2017). The clinimetric quality of the HADS is therefore assessed as good.

**Step 7 and 8 – Are standard values available and how do you calculate and interpret the data?**
The standard values of the recommended measurement instruments are included in the respective modules of this guideline. For the standard values and interpretation of optional measurement instruments, please refer to www.meetinstrumentenzorg.nl.

*Physical capacity/exercise capacity*
Standard values are available for the 6MINWT (Six Minute Walk Test) and various versions of the SWT (Andrianopoulos 2015; Beekman 2013, 2014; Troosters 1999; Wise 2005). With regard to the 6MWT, it is important for the standard values to be used that are associated with the way the test was taken, such as route length (Beekman 2013) and the manner of encouragement, and for the standard values to match the country or region where the tested person is from (Andrianopoulos 2015). For the CWRT, standard values are available for evaluating clinical progress (Puente-Maestu 2016). Standard values are also available for CPET (ERS 2019b). See B.5 'Patient profiles' for standard values and the interpretation of the 6MWT in relation to the profile classification. For standard values and interpretation of the CPET, see B.3.2 'Maximal exercise test'.

*Oxygen saturation*
With regard to oxygen saturation, recommendations have been formulated for the situation in which the training must be (temporarily) stopped due to excessively low oxygen saturation. See C.3.4 'Oxygen saturation and training with oxygen supplementation'.

*Dyspnoea*
Standard values are also available for the mMRC. An mMRC-score ≥ 2 is often used to differentiate between 'no/slight dyspnoea' and 'severe to very severe dyspnoea' (GOLD 2020). Additional research indicates that this cut-off point appears to overestimate the number of patients with slight dyspnoea and that a cut-off point of ≥1 is

more comparable to a CAT score of ≥ 10 (Jones 2013). An mMRC ≥ 2 corresponds better with the cut-off point ≥ 18 on the CAT; ≥ 1.9 points on the CCQ and ≥ 46.0 points on the SGRQ (Smid 2017).

***Fatigue***
Comprehensive standard data are available for the CIS20R from various groups of healthy persons and patients, including COPD patients (Vercoulen 1994, 1999). Cut-off points on the CIS8R are generally based on the average scores for healthy adults plus one or two standard deviations, or 27 to 35 points for increased fatigue and ≥ 35 points for severe fatigue (Van Hoogmoed 2010), with the latter score corresponding to the fatigue gradation of patients with chronic fatigue syndrome (Knoop 2008). No minimal clinically relevant difference was reported (Hewlett 2011).

***Muscle strength***
Standard values and reference formulas are available for HHD measurement (Ploeg 1991; McKay 2017; Andrews 1996; Bohannon 1997). There are no standard values for the 1RM tests, and the measured values are to a large extend dependent on the equipment used, due to which these tests cannot be used for diagnostic purposes.

***Nutritional status***
Standard values of the MUST and the SARC-F have been formulated for referral in connection with (an increased risk of) malnutrition or sarcopenia (GLIM 2019). See the recommendations in B.4.2 'Referral to other healthcare providers'.

***Respiratory muscle function***
Standard values are available for the MIP for determining decreased respiratory muscle function (ERS 2019a; Rodrigues 2017).

***Pain***
The clinically relevant difference when measuring pain with the help of the NPRS was determined among a population of patients with non-specific neck symptoms (Pool 2007).

***Balance and risk of falling***
Standard data are available for the TUG (Podsiadlo 1991; Van Wegen 2005). The risk of falling can be determined using these standard data.

***Physical activity***
Various studies have stated that a person must take at least 7,500 to 10,000 steps per day in order to speak of an active, healthy lifestyle (Hancock 2012; Lee 2019; Tudor-Locke 2004). However, it appears that a healthy person takes an average of 5,500 to 6,000 steps per day and people with a chronic illness take only 3,500 to 5,500 per day (Tudor-Locke 2001, 2004; Lee 2019). See B.5 'Patient profiles' for standard values and the interpretation of the activity meter in relation to the profile classification.

***Activities and participation in ADL***
See B.6 'Setting goals' for recommendations on the use of the PSG when setting goals.

***Symptom burden***
The symptom burden is determined by the pulmonologist, the general practitioner or the nursing specialist. See B.5 'Patient profiles' for standard values and the interpretation of the CCQ and CAT in relation to the profile classification.

***Anxiety and depression***
Standard data of the HADS are available (Smid 2017; Snaith 1994).

**Difference between recommended and optional measurement instruments**

The difference between the recommended and optional measurement instruments is based on the degree to which the measurement instrument is needed for the recommendations in this guideline.
The following measurement instruments are marked as recommended based on this:

- CCQ or CAT (symptom burden), 6MWT (physical capacity) and activity meter (physical activity). See B.5 'Patient profiles'.
- CPET for profiles 4, 5 and 6 (maximal exercise capacity). See B.3.2 'Maximal exercise test'
- PSG (activities and participation). See B.6 'Setting goals'
- Oxygen saturation meter (oxygen saturation). See C.3.4 'Training in relation to oxygen desaturation'.

Other measurement instruments are considered to be relevant but are marked as optional given that they are required to a lesser degree for following the recommendations in this guideline. The optional measurement instruments are included in the Explanation.

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### Note B.3.2 Maximal exercise test

#### Clinical question

**When are COPD patients referred for a maximal exercise test?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

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## Note B.4 Red flags and referral

### Note B.4.1 Red flags

**Clinical question**

**When is it necessary to refer a patient with COPD (back) to the general practitioner or pulmonologist?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

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### Note B.4.2 Referral to other healthcare providers

**Clinical question**

**When is referral to another specialty necessary (possibly through the general practitioner)?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

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## Note B.5 Patient profiles

### Clinical question

**Based on which traits of COPD patients are patient profiles differentiated in order to choose the right type of care?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

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## Note B.6 Setting goals

### Clinical question

**How can the therapist best set goals together with the patient?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

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## Note B.7 Diagnostic actions for sub-groups

### Note B.7.1 Diagnostic actions in the presence of co-morbidity

### Clinical question

**How are diagnostic actions defined if a COPD patient has a co-morbidity (and takes the related medication) that impacts their physical functioning?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

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## Note B.7.2 Diagnostic actions in the presence of an exacerbation

### Clinical question

**How is the diagnostic process for COPD patients with an exacerbation defined?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

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## Note B.7.3 Diagnostic actions in the palliative phase

### Clinical question

**How are the therapist's diagnostic actions defined for COPD patients in the palliative phase?**

In consultation with the guideline panel and the review panel, it was decided not to conduct a systematic search for this clinical question but rather to collect the information in a non-systematic manner. Ultimately, the following literature was used to answer the clinical question.

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# C Therapeutic process

## Note C.1 Counselling and advice

### Clinical question

**Which counselling and advice does the therapist give to COPD patients?**

### Literature

To answer the clinical question*, it was decided in consultation with the guideline panel and the review panel not to conduct a systematic review. The literature about this topic was collected in a non-systematic manner and is mentioned in the literature list below.

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* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

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## Note C.2 Optimisation of physical activity

### Clinical question

**How can the therapist optimise physical activity during ADL for COPD patients?**

### Literature

To answer the clinical question*, it was decided in consultation with the guideline panel and the review panel not to conduct a systematic review for pragmatic reasons. The literature about this topic was collected in a non-systematic manner and is mentioned in the literature list below.

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* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

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## Note C.3 Facilitation of physical capacity

### Note C.3.1 Endurance/interval training

#### Clinical questions

- **What is the best type of training to facilitate physical capacity in COPD patients: interval training or endurance training?**
- **How (FITT) should endurance/interval training be administered to COPD patients?**

#### Literature over endurance training of interval training

A systematic review was conducted for the first clinical question on the best type of training, endurance training or interval training.

**Outcome measures**

Quality of life, dyspnoea, exacerbations and physical functioning in ADL are listed as patient-relevant outcome measures crucial to the decision-making process. Physical exercise capacity, peripheral muscle strength and adverse events are listed as patient-relevant and important outcome measures for the decision-making process.

**Search and selection**

*Search*

Given the overlap of the clinical questions, a joint search was conducted for literature regarding all clinical questions on exercise therapy FITT principles. Due to the size of the topic, the search strategy on exercise therapy FITT principles was conducted in two steps: first a search for systematic reviews (SRs), and then a search for randomised controlled trials (RCTs) in order to update the most relevant SR.

A systematic search with relevant search terms on 29 May 2018 searched for SRs of RCTs in the following databases, among others: PubMed, EMBASE, Web of Science, Cochrane Library, CENTRAL and EmCare. The same databases were searched on 21 February 2019 for RCTs regarding exercise therapy FITT principles. The search rationale for SRs and RCTs is listed in appendix C.3.1.

*Literature selection*

Studies were selected based on the selection criteria in the following table.

| *Selection criteria* | |
|---|---|
| Type of studies | SRs and RCTs |
| Type of patients | adults with COPD |
| Type of interventions | any form of endurance/interval training |
| Type of comparisons | direct comparison of exercise therapy type: interval training versus endurance training |
| Type of outcomes (desirable and undesirable effects) | • 'crucial outcome measures': physical exercise capacity, quality of life, dyspnoea, exacerbations, physical functioning in ADL<br>• 'important outcome measures': peripheral muscle strength and adverse events |
| Type of timeline | immediately after the intervention |
| Other | availability of the complete text |

* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

The search strategy for SRs yielded 783 references. From these, the Beauchamp 2010 and Zainuldin 2011 SRs were selected as the most suitable for the clinical question. These SRs form the basis of this literature review. The search strategy for RCTs then yielded 1,607 references. Selection by title, summary and complete text did not yield any new recent RCTs that could be added to the systematic reviews of Beauchamp 2010 and Zainuldin 2011. Initially, the SR of Beauchamp (2010) and the Cochrane review of Zainuldin (2011) were included. However, the review of Beauchamp (2010) contained one study that was excluded in the review Zainuldin (2011). The reason for the exclusion was that the interval program included three days of interval training and two days of endurance training. Due to this, a clean comparison between interval training and endurance training could not be done. The Cochrane review of Zainuldin (2011) also contains a new RCT, which had not yet been published before the review of Beauchamp (2010). For this reason, the Cochrane review of Zainuldin (2011) was used to answer the clinical question.

**Literature summary**

***Description of studies***

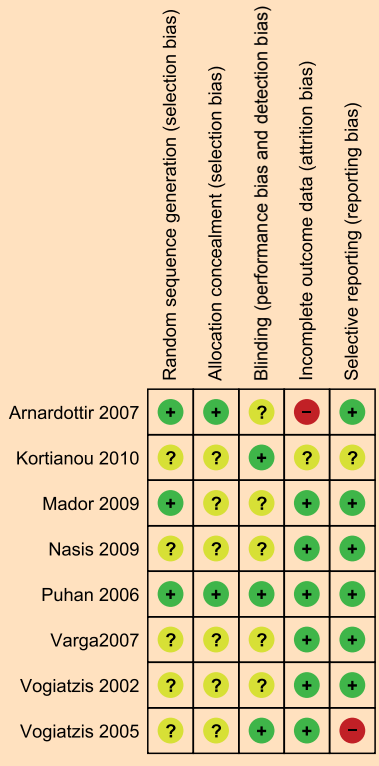
Endurance training and interval training were compared in eight of the 11 studies from the Zainuldin SR (2011). A total of 367 patients with stable COPD and an FEV1/FVC ratio of < 0.7 were included in these eight studies. On most of the studies, the endurance and interval training were conducted on a bicycle ergometer and in one study on a treadmill or bicycle ergometer. The endurance training consisted of moderate to high-intensity training (50-80% of the maximal cycle load) for 20-45 minutes, excluding warm-up and cool-down. The interval training consisted of high-intensity training (80-100% of the maximal cycle load) for 20-180 seconds, alternating with 30-180 seconds of moderate to low-intensity training (30-75% of the maximal cycle load) or rest. The total training duration for the interval training was 27 to 45 minutes. The treatment frequency was 2 to 5 times per week and the treatment duration 3 to 16 weeks.

Detailed information about the characteristics of the included studies is provided in the evidence table in appendix C.3.1.

***Individual study quality***

The study design and execution of all eight studies ('risk of bias', RoB) were assessed using the Cochrane RoB tool with low, high or unclear risk for six causes of bias, specifically random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues. An overview of the study quality assessment (RoB) per study is provided in the following table.

*Risk of bias: Interval training versus endurance training*




+ = yes; − = no; ? = unclear

***Results and evidentiary value per outcome measure***
The results were taken over from the Zainuldin review (2011).

*Functional physical capacity*
In five studies, the functional physical capacity was measured with the Six Minute Walk Test (6MWT). There was no significant difference between de groups (MD = -3.10; 95%-CI = -17.88 to 11.69).
For the functional physical capacity (6MWT) outcome measure, the evidentiary value was lowered by two levels due to limitations in study implementation (incomplete data of the outcome measure) and imprecision.
The evidentiary value is therefore *low*.

*Quality of life*
The quality of life in three studies was measured with the 'Chronic Respiratory Disease Questionnaire' (CRQ). There was no significant difference between de groups (MD = 2.51; 95%-CI = -1.32 to 6.34).
For the quality of life (CRQ) outcome measure, the evidentiary value was lowered by one level due to selective reporting in one study. The evidentiary value is therefore *moderate*.

*Muscle strength*
None of the studies measured muscle strength.

*Dyspnoea*
In five studies, dyspnoea was measured with the modified Borg Scale 'Fatigue' (scale: 0-10). There was no significant difference between de groups (MD = 0.09; 95%-CI = -0.18 to 0.35). In one study, dyspnoea was measured with the Borg Scale 'Fatigue' (scale: 6-20). There was no significant difference between de groups (MD = 0.2; 95%-CI = -0.15 to 0.55) in this study either.
For the dyspnoea outcome measure, the evidentiary value was lowered by two levels due to limitations in study design and execution. The evidentiary value is therefore *low*.

*Undesirable effects*
These were reported in one of the included RCTs, and no undesirable effects occurred in that RCT.
*Exacerbations*
None of the studies reported exacerbations.

*Physical functioning in ADL*
None of the studies measured physical functioning in ADL.

**Considerations**
The direction and strength of the recommendation are not only determined by findings in the literature. Other considerations also play a role, such as costs, acceptability and feasibility**.**

The considerations concerned:
**Desirable effects** The literature does not show any demonstrable differences between the effects of endu rance training and the effects of interval training in COPD patients.
**Undesirable effects** No undesirable effects of either types of training were reported in the included studies.
**Quality of desirable effects** The evidentiary value is low to moderate, depending on the outcome measure.
**Balance between desirable and undesirable effects** Given the lack of the effects found, this balance cannot be assessed.
**Value of desirable effects** Physical training, both endurance training and interval training, is effective in improving physical capacity in COPD patients (ATS/ERS 2013; ERS 2019).
**Variation in the value of desirable effects**Not all COPD patients are able to complete endurance training at the right intensity and/or duration (Maltais 1997; Puhan 2008). This can result in the training stimulus not being sufficient for increasing physical capacity. Often this concerns COPD patients with serious airflow limi tation and weakened thigh muscles (Spruit 2007). The right type of training can be chosen based on a maximal exercise test. The patient's goals and preferences must also be taken into account.
**Required resources (costs)** There is no difference in costs between the two types of training.
**Variation in required resources (costs)** There is no variation in required resources between the two types of training.
**Cost-effectiveness** Not applicable.
**Acceptability** Both types of training are acceptable for both the patient and the therapist, provided that the patient's capacity is taken into account.
**Feasibility** Both types of training are currently already frequently being applied and are deemed feasible.

### Literature about the endurance/interval training FITT principles

In consultation with the guideline panel and the review panel, it was decided for pragmatic reasons not to conduct a systematic search for answering the second clinical question but rather to collect the information in a non-systematic manner. The literature that was employed is included in the list of references.

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## Note C.3.2 Muscle strength training

### Clinical questions

1. **What is the value of muscle strength training for COPD patients?**
2. **How (FITT) should muscle strength training be administered to COPD patients?**
3. **What is the added value of whole body vibration during muscle strength training?**

### Literature about the value of muscle strength training as an additional type of training along with endurance/interval training

A systematic review was conducted to answer the clinical question* about the value of muscle strength training.

#### Outcome measures

Quality of life, dyspnoea, exacerbations, physical capacity (exercise capacity) and physical functioning in ADL are listed as patient-relevant outcome measures crucial to the decision-making process. Physical capacity (exercise capacity) is listed as a crucial outcome measure because strength training has an additional value for these outcome measures. Peripheral muscle strength and adverse events are listed as patient-relevant and important outcome measures for the decision-making process.

#### Search and selection

*Search*

Given the overlap of the clinical questions, a joint search was conducted for literature regarding all clinical questions on exercise therapy FITT principles (modules C.3.1 'Endurance/interval training', C.3.2 'Muscle strength training' and C.5.1 'Therapy duration and frequency'). Because this is an extensive topic, the search strategy on exercise therapy FITT principles was conducted in two steps: first a search for SRs was done and then a search for randomised controlled trials (RCTs) with the goal of updating the relevant SR.
A systematic search with relevant search terms on 29 May 2018 searched for SRs of RCTs in the following databases, among others: PubMed, EMBASE, Web of Science, Cochrane Library, CENTRAL and EmCare. In the same databases a search was conducted on 21 February 2019 for RCTs regarding exercise therapy FITT principles. The search rationales for SRs and RCTs on exercise therapy FITT principles (endurance, interval and muscle strength training) are listed in appendix C.3.1.

*Literature selection*

Studies were selected based on the selection criteria in the following table.

* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

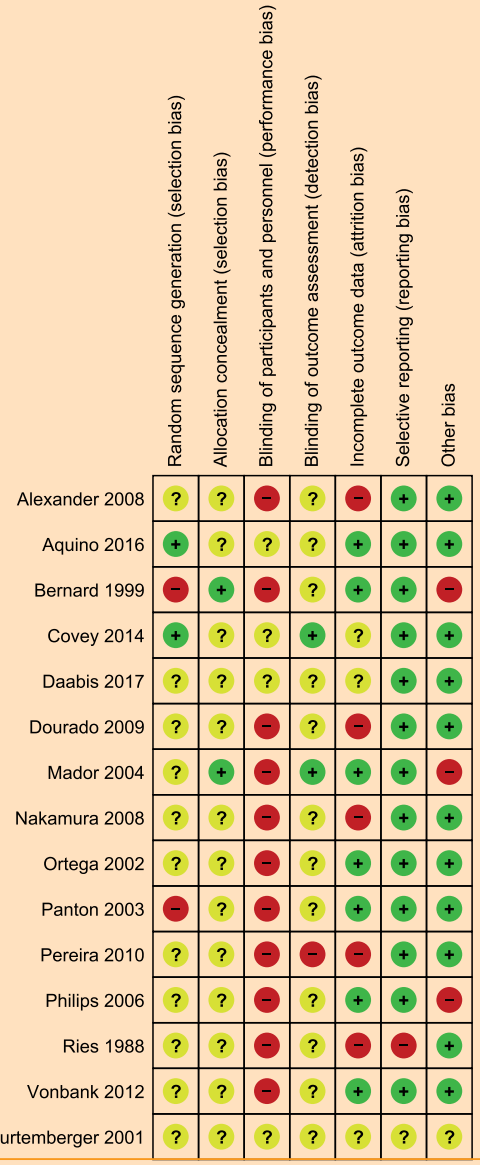
| *Selection criteria* | |
|---|---|
| Type of studies | SRs (search strategy 1) and RCTs (search strategy 2) |
| Type of patients | adults with COPD |
| Type of interventions | any form of endurance/interval training and strength training |
| Type of comparisons | ddirect comparison of exercise therapy type: cardiorespiratory training versus cardiorespiratory and strength training |
| Type of outcomes (desirable and undesirable effects) | • 'crucial outcome measures': physical capacity/exercise capacity, quality of life, dyspnoea, exacerbations, physical functioning in ADL<br>• 'important outcome measures': physical capacity, peripheral muscle strength and adverse events |
| Type of timeline | immediately after the intervention |
| Other | availability of the complete text |

The search strategy for SRs yielded 783 references. From these, the Iepsen SR (2015) was selected as the most suitable for the clinical question. This SR forms the basis of this literature review.
The search strategy for RCTs yielded 1,607 references. After selection by title, summary and complete text, four RCTs (Aquino 2016; Covey 2014; Daabis 2017; Pereira 2010) were added to Iepsen 2015.
The Iepsen 2015 SR contains 11 relevant RCTs. Subsequently, four recent RCTs were added to this. This literature review covers a total of 15 RCTs with a total of 494 participants.

***Description of studies***
The 15 included studies describe the effects of cardiorespiratory training and muscle strength training compared to only cardiorespiratory training in people with COPD. A total of 494 patients were included. Thirteen studies took place in a first-line setting and two studies during a stay in a rehabilitation facility. In one study (Aquino 2016), the exercise therapy frequency deviated significantly from that in the other 14 studies; in the deviating study training took place 10 times per week, compared to two to three times per week in the other studies.

***Individual study quality***
The study design and execution of all 15 studies ('risk of bias', RoB) were assessed using the Cochrane RoB tool with low, high or unclear risk for six causes of bias, specifically random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues. An overview of the study quality assessment (RoB) per study is provided in the following table.

*Risk of bias: Endurance/interval training versus strength and endurance/interval training*




\+ = yes; – = no; ? = unclear

***Results and evidentiary value per outcome measure***

*Functional physical capacity*

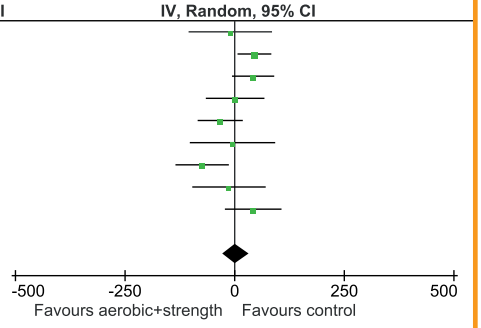
In nine studies, the functional physical capacity was measured by means of the 6MWT (Alexander 2008; Bernard 1999; Covey 2014; Daabis 2017; Dourado 2009; Mador 2004; Nakamura 2008; Philips 2006; Wurtemberger 2001). The meta-analysis of these 9 studies, which compared combination training (*n* = 133) to cardiorespiratory training alone (*n* = 135), does not show a clinically relevant difference between the groups (MD = 3.00 metres; 95%-CI = -26.86 to 32.85). See the forest plot.

The evidentiary value for the functional (physical) capacity outcome measure was lowered by two levels due to a limited study design and by one level due to imprecision. The evidentiary value is therefore very low.

*Forest plot of the effectiveness of muscle strength training on the functional physical capacity*

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Alexander 2008 | 365 | 105 | 10 | 375 | 112 | 10 | 6.9% | -10.00 [-105.15, 85.15] |
| Bernard 1999 | 499 | 68 | 21 | 454 | 50 | 15 | 16.6% | 45.00 [6.45, 83.55] |
| Covey 2014 | 398 | 89 | 35 | 356 | 115 | 35 | 14.4% | 42.00 [-6.18, 90.18] |
| Daabis 2017 | 348 | 97.3 | 15 | 347 | 89.3 | 15 | 10.7% | 1.00 [-65.83, 67.83] |
| Dourado 2009 | 559 | 52 | 11 | 592 | 76 | 13 | 13.7% | -33.00 [-84.49, 18.49] |
| Mador 2004 | 410 | 126.0317 | 11 | 415 | 115.3776 | 13 | 6.7% | -5.00 [-102.37, 92.37] |
| Nakamura 2008 | 499 | 64.52 | 10 | 573.2 | 84.5 | 13 | 11.8% | -74.20 [-135.10, -13.30] |
| Philips 2006 | 339 | 113.842 | 10 | 352 | 69 | 9 | 8.2% | -13.00 [-96.73, 70.73] |
| Wurtemberger 2001 (1) | 377.2 | 65.3 | 10 | 335 | 88.9 | 12 | 11.1% | 42.20 [-22.36, 106.76] |
| **Total (95% CI)** | | | **133** | | | **135** | **100.0%** | **3.00 [-26.86, 32.85]** |

Heterogeneity: Tau² = 1007.48; Chi² = 16.45, df = 8 (P = 0.04); I² = 51%
Test for overall effect: Z = 0.20 (P = 0.84)




Footnotes
(1) subgroup with supplemental oxygen

*Muscle strength*

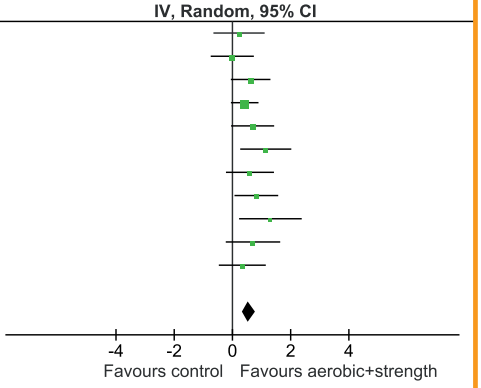
In the Iepsen SR (2015), 'leg press' and 'leg extension data' of eight studies were pooled, to which three recent RCTs were added (Alexander 2008; Aquino 2016; Bernard 1999; Covey 2014; Daabis 2017; Dourado 2009; Mador 2004; Ortega 2002; Panton 2003; Philips 2006; Vonbank 2012). These pooled data showed a reasonable effect in favour of the combination training (*n* = 162) compared to cardiorespiratory training alone (*n* = 160) (SMD = 0.56; 95%-CI = 0.34 tot 0.79). See the forest plot.

The evidentiary value for the muscle strength outcome measure was lowered by two levels due to a limited study design. The evidentiary value is therefore low.

*Forest plot of the effectiveness of muscle strength training on muscle strength*

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Alexander 2008 | 108 | 36 | 10 | 99 | 40 | 10 | 6.6% | 0.23 [-0.65, 1.11] |
| Aquino 2016 | 37.29 | 13.34 | 14 | 37.36 | 13.21 | 14 | 9.3% | -0.01 [-0.75, 0.74] |
| Bernard 1999 | 67 | 21 | 21 | 55 | 15 | 15 | 11.0% | 0.63 [-0.05, 1.31] |
| Covey 2014 | 387 | 118 | 35 | 341 | 97 | 35 | 22.7% | 0.42 [-0.05, 0.90] |
| Daabis 2017 | 24.1 | 2.1 | 15 | 22 | 3.6 | 15 | 9.3% | 0.69 [-0.05, 1.43] |
| Dourado 2009 | 116 | 32 | 11 | 85 | 20 | 13 | 6.6% | 1.14 [0.27, 2.02] |
| Mador 2004 | 55 | 19.8997 | 11 | 45 | 11.8983 | 13 | 7.5% | 0.60 [-0.22, 1.43] |
| Ortega 2002 | 55 | 10 | 14 | 47 | 9 | 16 | 9.0% | 0.82 [0.07, 1.57] |
| Panton 2003 | 841 | 342 | 9 | 460 | 176 | 8 | 4.4% | 1.30 [0.23, 2.38] |
| Philips 2006 | 102 | 41.1096 | 10 | 76 | 27 | 9 | 5.8% | 0.71 [-0.23, 1.64] |
| Vonbank 2012 | 136.2 | 139.6033 | 12 | 94.9 | 90.4131 | 12 | 7.8% | 0.34 [-0.47, 1.15] |
| **Total (95% CI)** | | | **162** | | | **160** | **100.0%** | **0.56 [0.34, 0.79]** |

Heterogeneity: Tau² = 0.00; Chi² = 7.68, df = 10 (P = 0.66); I² = 0%
Test for overall effect: Z = 4.89 (P < 0.00001)




*Quality of life*

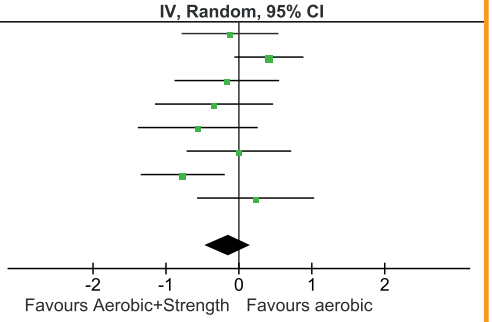
In eight studies, the quality of life was measured using the St. George's Respiratory Questionnaire (SGRQ) or the CRQ (Bernard 1999; Covey 2014; Daabis 2017; Dourado 2009; Mador 2004; Ortega 2002; Pereira 2010; Vonbank 2012). Data from these studies were pooled, and a comparison was made between combination training (*n* = 144) and cardiorespiratory training alone (*n* = 144). No clinically relevant difference was demonstrated between the groups (SMD = -0.14 (95%-CI = -0.46 to 0.17). See the forest plot.

The evidentiary value for the quality of life outcome measure was lowered by two levels due to limitations in the study design and execution and by one level due to imprecision. The evidentiary value is therefore very low.

*Forest plot of the effectiveness of muscle strength training on quality of life*

| Study or Subgroup | Aerobic+ strength Mean | SD | Total | Aerobic Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bernard 1999 | 1 | 0.8 | 21 | 1.1 | 0.8 | 15 | 13.0% | -0.12 [-0.79, 0.54] |
| Covey 2014 | 4.5 | 1.2 | 35 | 4 | 1.2 | 35 | 18.1% | 0.41 [-0.06, 0.89] |
| Daabis 2017 | 46.4 | 17.7 | 15 | 49.4 | 17.7 | 15 | 11.8% | -0.16 [-0.88, 0.55] |
| Dourado 2009 | 33 | 17 | 11 | 39 | 17 | 13 | 10.1% | -0.34 [-1.15, 0.47] |
| Mador 2004 | 4.2 | 0.995 | 11 | 4.7 | 0.7211 | 13 | 9.9% | -0.56 [-1.39, 0.26] |
| Ortega 2002 | 4.3 | 1.2 | 14 | 4.3 | 1.1 | 16 | 11.8% | 0.00 [-0.72, 0.72] |
| Pereira 2010 | 34.8 | 11.5 | 25 | 44.4 | 13 | 25 | 15.1% | -0.77 [-1.35, -0.19] |
| Vonbank 2012 | 31.6 | 54.39 | 12 | 19.1 | 50.58 | 12 | 10.2% | 0.23 [-0.57, 1.03] |
| **Total (95% CI)** | | | **144** | | | **144** | **100.0%** | **-0.14 [-0.46, 0.17]** |

Heterogeneity: Tau² = 0.08; Chi² = 11.99, df = 7 (P = 0.10); I² = 42%
Test for overall effect: Z = 0.90 (P = 0.37)




*Dyspnoea*

In the Daabis RCT (2017), dyspnoea is measured using the modified Medical Research Council Dyspnoea questionnaire (mMRC). No clinically relevant difference was found between combination training (*n* = 15; 46% improvement compared to baseline) and cardiorespiratory training alone (*n* = 15; 44% improvement compared to baseline).

The evidentiary value for the dyspnoea outcome measure was lowered by two levels due to a limited study design and by one level due to imprecision. The evidentiary value is therefore very low.

*Undesirable effects*

Potential undesirable effects were seen in four RCTs (*n* = 105; Bernard 1999; Panton 2004; Philips 2006; Ries 1988). Undesirable effects did not occur in two of the RCTs and did occur in two others: two cases of backache, possibly due to the combination training, and one case of hip pain, possibly due to the cardiorespiratory training. The evidentiary value for the undesirable effects outcome measure was lowered by two levels due to a limited study design and by one level due to imprecision. The evidentiary value is therefore very low.

*Exacerbations*

None of the studies reported exacerbations.

*Physical functioning in ADL*

None of the studies measured physical functioning in ADL.

## Considerations

The direction and strength of the recommendation are not only determined by findings in the literature. Other considerations also play a role, such as costs, acceptability and feasibility.

**Desirable effects** The literature describes a reasonable effect of muscle strength training on muscle strength when these are combined with cardiorespiratory training. No effect of muscle strength training was found on physical capacity, quality of life and dyspnoea.

**Undesirable effects** Only mild undesirable effects (backache) of muscle strength training were reported in the included studies.

**Quality of desirable effects** The evidentiary value is very low to low, depending on the outcome measure.

**Balance between desirable and undesirable effects** The positive effects on muscle strength likely outweigh the small risk of undesirable effects, such as backache.

**Value of desirable effects** Muscle strength training of the larger muscle groups of the lower extremity as a standalone intervention is an effective training method for increasing muscle mass and strength, which helps increase physical capacity (Li 2019). The big advantage of muscle strength training is the relatively low workload on the limited respiratory system, due to which COPD patients experience a lot fewer symptoms of dyspnoea during strength training compared to endurance training (Probst 2006; Sillen 2008).

**Variation in value of desirable effects** Weakening of the muscle groups of the lower extremity can contribute to premature stopping of physical activity in COPD patients (Gosselink 1996; Man 2003; Singer 2011). This can be expressed during a maximal cycle test by symptom scores of ≥ 7 points on a 0–10 Borg Scale. In addition, these patients will have a decreased function of the quadriceps muscles in specific muscle strength tests (Robles 2011; Seymour 2010). Muscle strength training can therefore be very valuable in particular for patients who cannot handle heavy workloads.

**Required resources (costs)** The muscle strength training often takes place with the assistance of training equipment that allows the therapist to properly set the training intensity after determining the 1RM. Purchasing this equipment is associated with relatively high costs, but the equipment is already present in lots of practices.
**Variation in required resources (costs)** There is no variation in required resources.
**Cost-effectiveness** No studies available.
**Acceptability** Muscle strength training is acceptable for both the patient (especially those who cannot handle heavy workloads) and the therapist.
**Feasibility** Muscle strength training is currently already frequently being applied and is deemed feasible.

### Literature about the application of muscle strength training (FITT principles)

To answer the question of how muscle strength training should be performed (FITT), a decision was made, in consultation with the guideline panel and the review panel, for a non-systematic manner of information collection and review.

### Literature about the added value of whole body vibration during muscle strength training

When answering the clinical question about the desirable and undesirable effects of whole body vibration for strength exercises with COPD patients compared to strength exercises on the floor, the recent SR of Zhou 2018 was taken over.

#### Outcome measures

Quality of life, physical capacity, balance and undesirable effects are listed as patient-relevant outcome measures crucial to the decision-making process.

#### Search and selection

The systematic review (SR) of Zhou 2018 is quite pertinent to the clinical question and is very recent. That is why it was decided to incorporate this SR and not to conduct an additional systematic review.

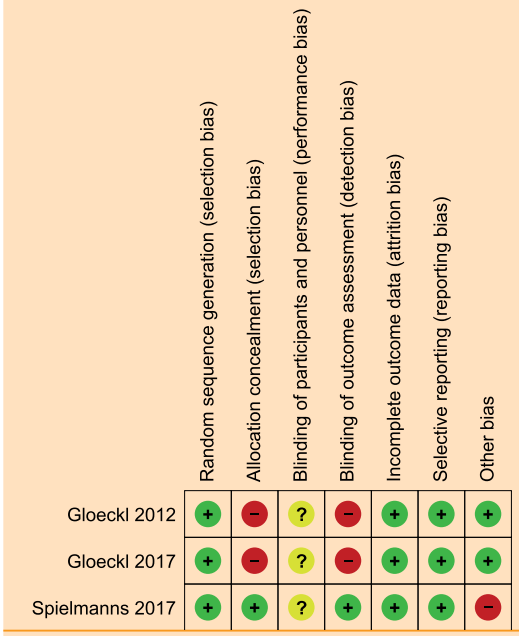
*Description of studies*

The Zhou 2018 SR includes three RCTs that compare the effectiveness of strength exercises (squats) on whole body vibration with the effectiveness of the same squats on the floor (Gloeckl 2012, 2017; Spielmans 2017). The three studies included a total of 172 patients. The number of sessions varied between nine (3x/wk for 3 weeks) and 13 (1x/wk for 3 months). A side alternating platform was used at a frequency of 24-26 Hz and an amplitude of 3 to 6 mm. The strength exercises consisted of squats in sets 4x2 min. or 3x3 min. or squats for 90 min.

*Individual study quality*

The design and implementation of the individual studies ('risk of bias'; RoB) was assessed by Zhou (2018) with the help of the Cochrane Risk-of-Bias tool. Information about blinding patients and healthcare personnel was not reported in any study. Other frequent potential causes of bias concern limitations in allocation concealment and blinding of outcome assessors. An overview of the study quality assessment (RoB) per study is provided in the following table.

*Risk of bias: Added value of whole body vibration during muscle strength training (Source: Zhou 2018)*




\+ = yes; − = no; ? = unclear

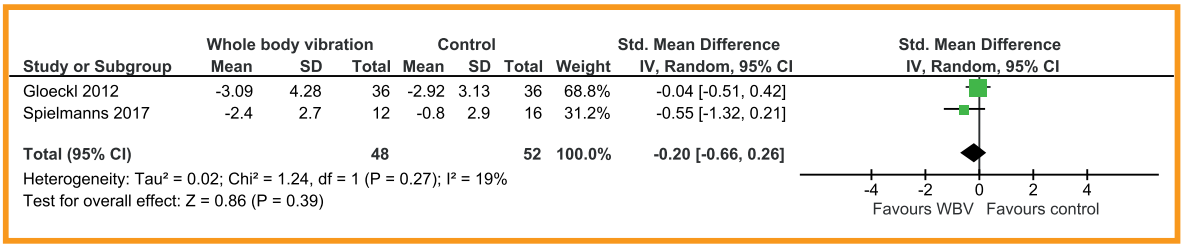
***Results and evidentiary value per outcome measure***

***Quality of life***

The effects of whole body vibration on quality of life are measured with the disease-specific questionnaires COPD Assessment Test (CAT; Spielmanns 2017) and the Chronic Respiratory Disease Questionnaire (CRQ; Gloeckl 2012). The two questionnaires have a different direction. While a high score on the CAT indicates a bad quality of life, a high score on the CRQ indicates a good quality of life. The outcomes of the QRQ were rescored to be able to combine the results of both questionnaires. The two studies (*n* = 100) show a small, insignificant quality of life improvement (SMD = −0.20; 95%-CI = −0.66 to 0.26). See the forest plot.

The evidentiary value for the quality of life was lowered by two levels given the limitations of the study design and execution (RoB) and the small number of patients (imprecision). The evidentiary value is therefore low.

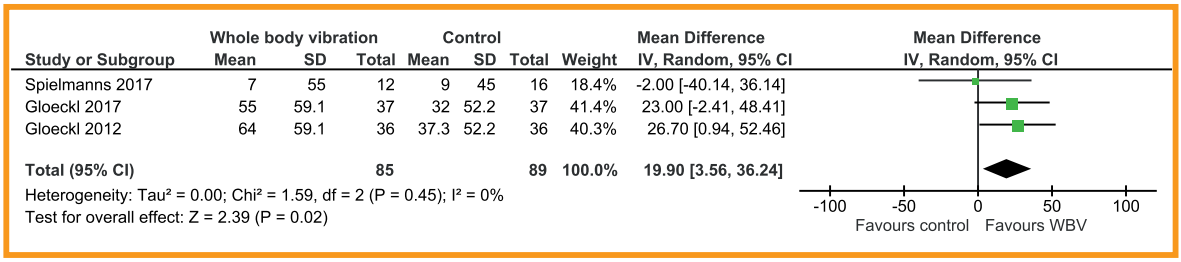
*Forest plot of the effectiveness of whole body vibration on quality of life*




***Physical capacity***

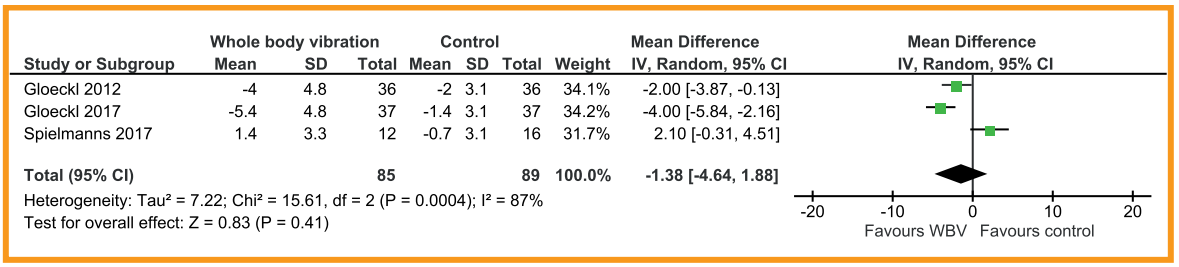
The physical capacity, also called the functional physical functioning, was measured in all three studies with the 6MWT and the 'Sit to Stand Test' (SST) (5 repetitions). Training on a vibration platform showed a small, significant but not clinically relevant improvement of the walking distance. Patients who trained on the vibration platform improved their walking distance measured by the 6MWT by 20 metres more than patients who did squats on solid ground (MD = 19.90 metres; 95%-CI = 3.56 to 36.24). See the forest plot.

*Forest plot of the effectiveness of whole body vibration on physical capacity: 6MWT in metres*




Training on a vibration platform showed a small, insignificant decrease in the time the patients needed to perform the SST five times (5x standing up from a chair and sitting down again) compared to training without a vibration platform (MD = −1.38 sec; 95%-CI = −4.64 to 1.88). See the forest plot.
The evidentiary value for physical capacity was lowered by two levels given the limitations of the study design and execution (RoB) and the small number of patients (imprecision). The evidentiary value is therefore low.

*Forest plot of the effectiveness of whole body vibration on physical capacity: SST in seconds*




*Balance*

The balance was measured in one study (Gloeckl 2017; *n* = 74). For this balance test, patients were asked to sit as still as possible during 10 seconds in four different positions. Patients who trained on a vibration platform showed a decrease in body swaying in all positions. The differences between whole body vibration and control group were:

- Romberg stance with eyes closed; MD = −76 mm (95%-CI = −202 to 30);
- stance with one foot forward (semi-tandem) and eyes closed, MD = −348 mm (95%-CI = −504 to-193);
- stance with one foot forward (semi-tandem) and eyes open, MD = −78 mm (95%-CI = −155 to −1);
- stance on one leg with eyes closed; MD = −187 mm (95%-CI = −327 to −48);

The evidentiary value for balance was lowered by three levels given the limitations of the study design and execution (RoB) and the very small number of patients (two levels; imprecision). The evidentiary value is therefore *very low*.

*Undesirable effects*

Adverse events were reported in one study (Spielmanns 2017; *n* = 28). No adverse events were observed in this study (RD = 0).
The evidentiary value for preventing adverse events was lowered by three levels given the limitations of the study design and execution (RoB) and the very small number of patients (two levels; imprecision). The evidentiary value is therefore very low.

An overview of the effects and the evidentiary value for all outcomes is provided in the following table.

*GRADE evidence profile of whole body vibration with strength exercises compared to strength exercises without whole body vibration for COPD patients*

| RCTs (*n*) | Quality assessment | | | | | Summary of results | | | GRADE |
|---|---|---|---|---|---|---|---|---|---|
| | Study design and execution (RoB) | Inconsistency | Indirectness | Imprecision | Publication bias | Patients (*n*) | | Effect size (95%-CI) | |
| | | | | | | I | C | | |
| **Quality of life** | | | | | | | | | |
| 2 | 1 level | none | none | 1 level | none | 48 | 52 | SMD = -0.20 (-0.66 to 0.26) | low |
| **Physical capacity/functional physical functioning** | | | | | | | | | |
| 3 | 1 level | none | none | 1 level | none | 85 | 89 | 6MWT: MD = 92 (21,4 tot 162,6) m | low |
| 3 | 1 level | none | none | 1 level | none | 85 | 89 | SST: MD = -1,38 (-4,64 tot 1,88) sec. | low |
| **Physical capacity/balance** | | | | | | | | | |
| 1 | 1 level | none | none | 2 levels | none | 37 | 37 | Romberg stance/eyes closed: MD = -76 (-202 to 30) mm<br>semi-tandem/eyes closed: MD = -348 (-504 to -193) mm<br>Semi-tandem/eyes open: MD = -78 (-155 to -1) mm<br>Stance on one leg/eyes open: MD = -187 (-327 to -48) mm | very low |
| **Adverse events** | | | | | | | | | |
| 1 | 1 level | none | none | 2 levels | none | 12 | 16 | RV = 0 | very low |

I = intervention group; C = control group. 6MWT = Six Minute Walk Test; IQR= (interquartile range); MD = mean difference; SMD = standardized mean difference; RD = risk difference; SST = Sit to Stand Test.

### Considerations

The direction and strength of the recommendation are not only determined by findings in the literature. Other considerations also play a role, such as costs, acceptability and feasibility.

The considerations concerned:

**Desirable effects** The effects of whole body vibration on physical capacity are low. For balance the effects of whole body vibration are reasonable.

**Undesirable effects** No undesirable effects of whole body vibration were reported in the included studies.

**Quality of desirable effects** The quality of the included literature with regard to the desirable effects is low to very low, depending on the outcome measure.

**Balance between desirable and undesirable effects** Given that no undesirable effects were reported, the desirable effects of the intervention outweigh the undesirable effects.

**Value of desirable effects** The effects on the crucial outcome measure physical capacity are small, so not much value is attached to this.

**Variation in value of desirable effects** Whole body vibration can have added value for patients with balance problems. However, the expectation is that instead of a vibration platform other training attributes can also be used that – in contrast to the vibration platform – the therapist does have at his disposal.

**Required resources (costs)** The costs of a vibration platform are relatively high compared to alternative training attributes whose goal is to improve balance.

**Variation in required resources (costs)** The costs of a vibration platform vary but are relatively high compared to alternative training attributes whose goal is to improve balance.

**Cost-effectiveness** There are no studies available on the cost-effectiveness of whole body vibration. Given the small effects, the expectation is that training with the assistance of a vibration platform is not more cost-effective than regular types of training.

**Acceptability** Given the limited added value of the vibration platform and the relatively high costs, the expectation is that application of the vibration platform is not acceptable for may therapists.

**Feasibility** Given the limited acceptability, use of a vibration platform in practice is not expected to be feasible. Therapists who have the opportunity to train with a vibration platform can consider using it if a patient has balance problems. However, it is also possible to use other attributes for this.

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## Note C.3.3 Hydrotherapy

### Clinical question

**Does hydrotherapy have added value for COPD patients compared to conservative therapy for improving physical capacity?**

### Literature

To answer this clinical question*, the systematic review of McNamara 2013a was used.

**Search and selection**

It was decided in consultation with the guideline panel and the review panel not to update the systematic review (McNamara 2013a).

**Literature summary**

The systematic review of McNamara 2013a included five (quasi-)randomised controlled studies (RCTs) with a total of 176 patients. Four of these studies compared hydrotherapy with training on land.

The meta-analysis of these studies does not show any differences in quality of life, which is measured here with the St. George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory (Disease) Questionnaire (CRDQ) (SMD = -0.14; 95%-CI = -0.57 to 0.28; *n* = 89; low evidentiary value).

There was also no difference in physical capacity measured with the Six Minute Walk Test (6MWT) (MD = 11 metres; 95%-CI = -11 to 33; *n* = 62; the evidentiary value is moderate) or the Incremental Shuttle Walk Test (ISWT; MD = 9 metres; 95%-CI = -15 to 34; *n* = 59; the evidentiary value is low), but there was a difference when the physical capacity was measured with the Endurance Shuttle Walk Test (ESWT; MD = 313 m; 95%-BI = 232 to 394; *n* = 59; the evidentiary value is moderate). Adverse events were reported in two studies (*n* = 20).

One non-serious incident during hydrotherapy was described in these studies.

### Considerations

The effects of hydrotherapy are largely the same as that of training on land. The costs of acquiring and maintaining a swimming pool are high. There are also practical objections, such as the space a swimming pool with the associated facilities requires and the time it costs patients to start with the training. However, hydrotherapy is an acceptable type of training for COPD patients (McNamara 2015). However, because the right facilities

* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

aren't just simply available everywhere, hydrotherapy is hardly used nowadays (Spruit 2014). Overall, the benefits of hydrotherapy do not outweigh its cost and practical objections. Hydrotherapy should only be considered for patients with additional physical problems that severely limit conventional training on land, such as joint osteoarthritis and/or pronounced obesity and/or if the patient has a strong preference for physical training in the form of hydrotherapy.
The considerations and recommendations stem from the deliberations held in the guideline panel based on the evidence-to-decision form. See appendix C.3.3.

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## Note C.3.4 Training in relation to oxygen desaturation

### Clinical question

The clinical question about transcutaneously measured oxygen saturation (Sp02) and use of medical oxygen during physical activity (test/exercise therapy) in patients with stable COPD is divided into the following sub-questions:

- **What is the minimum transcutaneously measured resting Sp02 with which a COPD patient may start a physical test or exercise therapy?**
- **To what extent is medical oxygen supplementation during a physical test or exercise therapy useful for COPD patients?**
- **At what transcutaneously measured Sp02 is the physical test or exercise therapy stopped?**

### Literature

To answer the three clinical sub-questions*, it was decided in consultation with the guideline panel and the review panel not to conduct a systematic review. The literature about this topic was collected in a non-systematic manner and is mentioned in the literature list below.

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Jarosch I, Gloeckl R, Damm E, Schwedhelm AL, Buhrow D, Jerrentrup A, et al. Short-term effects of supplemental oxygen on 6-min walk test outcomes in patients with COPD: a randomized, placebo-controlled, single-blind, crossover trial. Chest. 2017;151(4):795-803.
Nonoyama ML, Brooks D, Lacasse Y, Guyatt GH, Goldstein RS. Oxygen therapy during exercise training in chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2007;(2):CD005372.

* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

Walsh JA, Maddocks M, Man WD. Supplemental oxygen during exercise training in COPD: full of hot air? Eur Respir J. 2019;53(5).

## Note C.3.5 Neuromuscular electrical stimulation (NMES)

### Clinical question

1. **When is neuromuscular electrical stimulation (NMES) indicated for COPD patients?**
2. **What is the best way to administer NMES?**

### Literature about when NMES is indicated

To answer the first clinical question,* a systematic review was carried out according to the following review questions (PICO):

1. What are the effects of treatment with NMES (standalone) in patients with stable COPD without exer cise therapy?
2. What are the effects of treatment with NMES (add-on) in patients with stable COPD in addition to the exercise therapy?
3. What are the effects of treatment with NMES in patients who were admitted to the hospital (IC or HC) with a COPD exacerbation?

**Outcome measures**

Quality of life, physical functioning (e.g. the time until specific mobility milestones are achieved), dyspnoea, (functional) exercise capacity, peripheral muscle strength, length of hospital stay (if applicable), mortality and adverse events are listed as patient-relevant and crucial to the decision-making process.

**Search and selection**

*Search*

A systematic search with relevant search terms on 7 June 2018 searched for randomised controlled studies (RCTs) in the following databases, among others: PubMed, EMBASE, CENTRAL, Cochrane Library, Web of Science, PeDRO, Psychinfo and EmCare. The justification for the review is included in appendix C.3.5.

*Literature selection*

The studies were selected based on the following selection criteria: RCT, published in English or Dutch, on the desirable effects (quality of life, (functional) exercise capacity) and/or undesirable effects (adverse events and mortality) of NMES (NMES as a standalone intervention or in combination with exercise therapy (add-on)) in COPD patients compared to the usual care (without exercise therapy) or only exercise therapy.
The recent literature study by Hill (2018) on the effectiveness of NMES in people with COPD was used as a starting point. The 16 RCTs in this review were tested according to the selection criteria of this clinical question. One study reported no relevant outcome measures (Giavedon 2012) and is therefore not included. The other 15 studies are included in the review.
The literature search yielded another 115 hits. The articles that were published from March 2018 were reviewed using the selection criteria based on title, abstract and complete text. As of this update, one article (Bonnevie 2018) was added to the review. The total number of studies in this review therefore amounts to 16.
The articles that are based on the complete text are excluded, and the reasons for the exclusion are included in the appendix.

**Literature summary**

*Description of studies*

The review of the 16 studies concerned a total of 329 COPD patients. The average age of the patients varied between 56 and 76 years. The effectiveness of NMES was investigated in both patients with a stable clinical presentation (13 studies) and patients who were hospitalised due to an exacerbation (3 studies).
In 13 of the 16 studies the COPD patients had a stable clinical presentation. NMES was administered in various settings in these studies: at home (Akinlabi 2013; Bonnevie 2018; Latimer 2013; Maddocks 2016; Tardif 2015; Vieira 2014; Vivodtzev 2012), both as outpatient treatment and at home (Neder 2002), as outpatient treatment (Bourjeily-Habr 2002; Dang 2011; Tasdemir 2015), or as part of intramural rehabilitation (Kucio 2016; Vivodtzev

* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

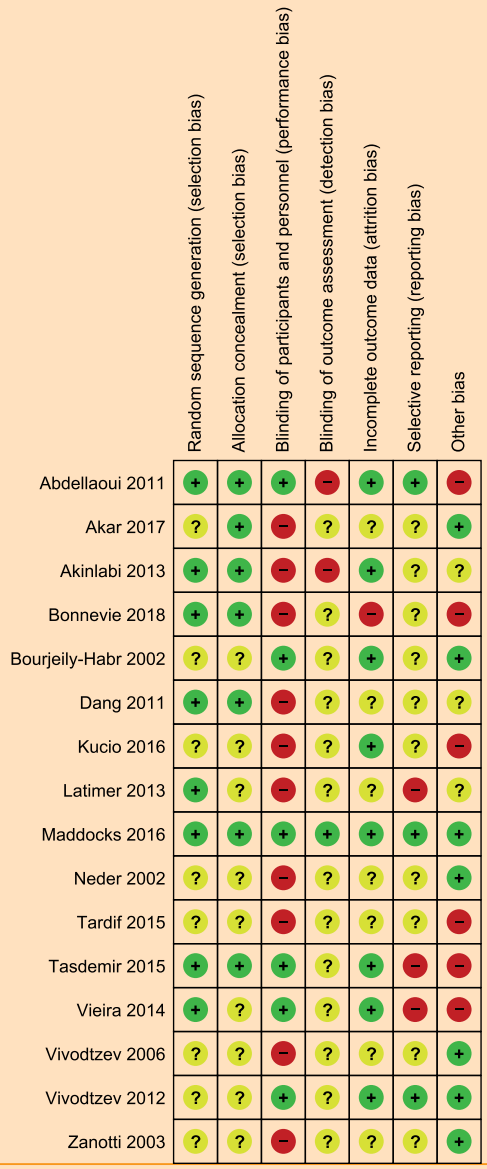
2006). Six of the 13 studies investigated the effectiveness of NMES as a standalone intervention compared to the usual medical care (Bourjeily-Habr 2002; Latimer 2013; Maddocks 2016; Neder 2002; Vieira 2014; Vivodtzev 2012). In the other seven studies, the effectiveness of NMES as an add-on to exercise therapy was investigated compared to exercise therapy without NMES (Akinlabi 2013; Dang 2011; Kucio 2016; Tardif 2015; Tasdemir 2015; Vivodtzev 2006; Bonnevie 2018). Administration of NMES as a standalone intervention and as an add-on intervention in combination with exercise therapy were analysed separately.
Three of the 16 studies investigated the effectiveness of NMES in COPD patients who were admitted to intensive care due to an exacerbation (IC; Abdellaoui 2011; Akar 2017) or who were admitted to high care after IC admission (HC; Zanotti 2003). The patients underwent invasive ventilation in two studies (Akar 2017; Zanotti 2003). The study by Abdellaoui (2011) concerned patients who received oxygen supplementation, non-invasive ventilation and invasive ventilation. In the Akar (2017) and Zanotti (2003) studies, mobilisation with NMES was compared to active mobilisation without NMES. In the Abdellaoui (2011) study, active-passive mobilisation with NMES was compared to active-passive mobilisation with placebo NMES, often in bed-ridden patients with severely weakened muscle function, severe functional impairment and a long period of immobility. Given the vulnerable health, deteriorated condition, clear muscle atrophy and long-term bed-ridden state of these patients, the results of these three studies were analysed separately. In one study all participants received unilateral NMES and the other leg (without NMES) served as the control leg (Latimer 2013). This study hence also randomised per leg instead of per participant. In the other studies, the participants were randomised and received bilateral NMES in the intervention group. All studies stimulated the femoral quadriceps muscles, sometimes in combination with the hamstrings (Abdellaoui 2011; Akinlabi 2013), the calf muscles (Kucio 2016), the hamstrings and the calf muscles (Bourjeily-Habr 2002; Vivodtzev 2012) of the gluteal muscles (Zanotti 2003).
The stimulation frequencies were 35 Hz (Abdellaoui 2011; Bonnevie 2018;
Kucio 2016; Tardif 2015; Vivodtzev 2006; Zanotti 2003), 45 Hz (Dang 2011) and 50 Hz (Akar 2017; Akinlabi 2013; Bourjeily-Habr 2002; Latimer 2013; Maddocks 2016; Neder 2002; Tasdemir 2015; Vieira 2014; Vivodtzev 2012).
The pulse duration varied between 200 µs (Bourjeily-Habr 2002) and 400 µs (Abdellaoui 2011; Bonnevie 2018; Vivodtzev 2006, 2012).
There were 11 studies that reported information about the series time; this information was not described in the Abdellaoui (2011), Akinlabi (2013), Tardif (2015) and Zanotti (2003) studies. There was no fixed series time in three studies (Maddocks 2016; Neder 2002; Vieira 2014), but rather the series time increased during the study period: from 2 sec stimulation and 15 or 18 sec rest in the first week, to 10 sec stimulation and 15 sec or 30 sec rest in the third week. In the other studies, the series time remained the same during the entire study period. This series time varied from very short cycles such as 0.5 sec stimulation and 1.5 sec rest in the Bonnevie (2018) study and 2 sec stimulation and 4 sec rest in the Kucio (2016) study to longer cycles such as 10 sec stimulation and 20 sec rest in the Tasdemir (2015) study and 15 sec stimulation and 5 sec rest in the Latimer (2013) study.
In most studies, the intensity of the stimulation was set to the maximum current that the patient found acceptable. In one study, the intensity was sufficient for generating a muscle contraction, and that intensity increased by 5 mA per week (Bourjeily-Habr 2002); in another study, the set intensity was equal to a muscle contraction corresponding to 15 to 25% of the maximum voluntary contraction (Maddocks 2016).
Most studies stimulated the muscles once or twice per day for 30 to 60 minutes, three to seven days per week for four to eight weeks.

A detailed overview of the included studies is available online as 'Appendix Evidence Tables'.

***Individual study quality***
The design and execution of the individual studies ('risk of bias'; RoB) was assessed with the help of the Cochrane Risk-of-Bias tool. The lack of blinding of patients and care personnel was the most common potential cause of bias.

An overview of the study quality assessment (RoB) per study is provided in the following table.

*Risk of bias: NMES*




\+ = yes; − = no; ? = unclear

**Results and evidentiary value**

The results and evidentiary value of the following are described below:

- NMES without exercise therapy (standalone) in patients with stable COPD compared to usual care;
- NMES in combination with exercise therapy (add-on) compared to exercise therapy alone in patients with stable COPD;
- NMES in combination with mobilisation in patients who were hospitalised with a COPD exacerbation (IC or HC).

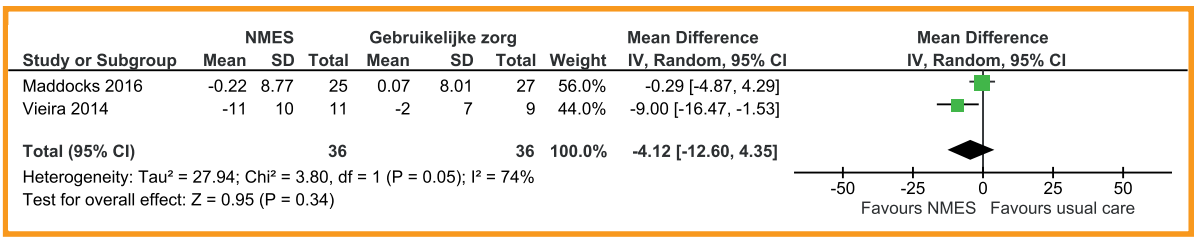
**NMES without exercise therapy (standalone) in patients with stable COPD compared to usual care**

*Quality of life*

The effect of NMES on the quality of life compared to usual care was reported in two studies (Maddocks 2016; Vieira 2014). Both studies used the St. George's Respiratory Questionnaire (SGRQ) The studies found a small, clinically relevant improvement of the quality of life; the SGRQ score of patients with NMES treatment was on

average 4.12 points lower than that of patients who received the usual care (95%-CI = −12.60 to 4.35; *n* = 72). A difference of 4 points is internationally considered to be clinically relevant (Jones 2005). See the forest plot. The evidentiary value for the quality of life was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision). The evidentiary value is therefore *low*.

***Forest plot of treatment with NMES (standalone) in patients with stable COPD: quality of life***




***Physical functioning***

Effects of NMES on physical functioning were not investigated in any of the included studies.

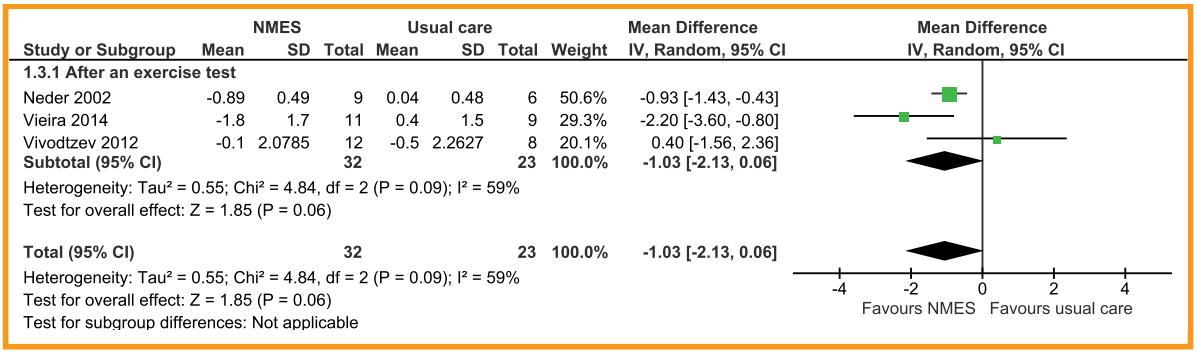
***Dyspnoea***

Treatment with NMES results in a large decrease of dyspnoea (Neder 2002; Vieira 2014; Vivodtzev 2012). The effects of NMES on dyspnoea after the end of a symptom-limited exercise test was studied in all three studies with the Borg Scale. Patients who were treated with NMES scored an average of 1.0 point lower on the Borg Scale (95%-CI = −2.13 to 0.06) than patients in the control group.

The Neder (2002) study also shows a large, clinically relevant decrease of dyspnoea in daily life, which is measured in this study with the 'Dyspnoea' domain of the Chronic Respiratory Disease Questionnaire (CRDQ). After six weeks of treatment, there was an average of 1.2 points (95%-CI = 0.4 to 2.0) difference between the group with NMES and the control group that received usual care. A difference of 0.5 points per domain is seen as a clinically relevant change in health status (Gyatt 1987). See the forest plot.

The evidentiary value for the effect of NMES on dyspnoea was lowered by three levels given the limitations of the study design and execution, the inconsistency of the results and the small number of patients (imprecision). The evidentiary value is therefore *very low*.

***Forest plot of treatment with NMES (standalone) in patients with stable COPD: dyspnoea***




***Functional exercise capacity***

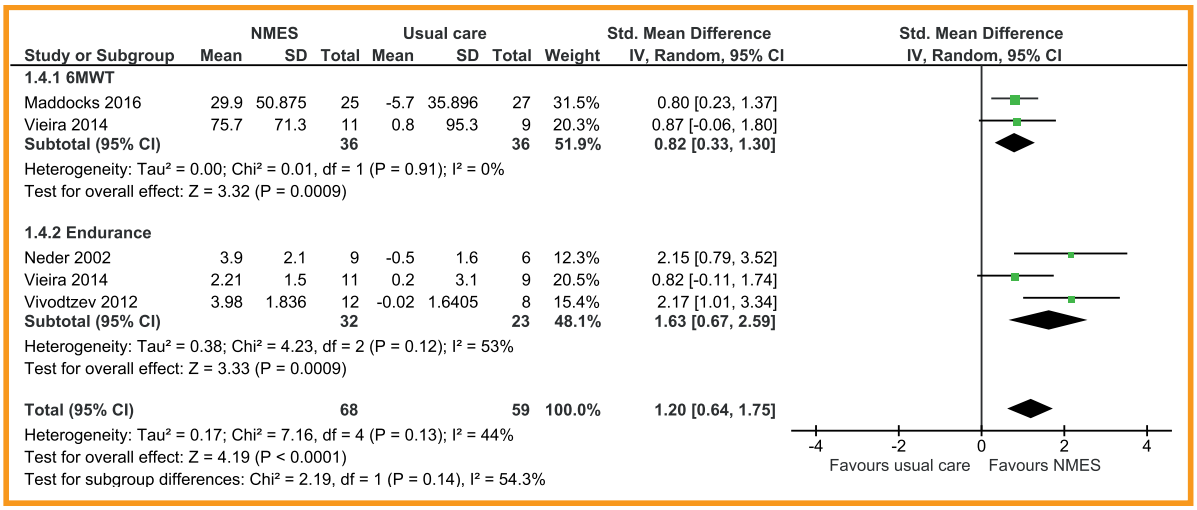
Five of the six studies on the effect of NMES on functional exercise capacity report sufficient data for a meta-analysis. This meta-analysis shows a large to very large improvement of the exercise capacity (SMD = 1.20; 95%-CI = 0.64 to 1.75; *n* = 127).

Two of the studies (Maddocks 2016; Vieira 2014) show a significant clinically relevant improvement in the Six Minute Walk Test (6MWT). Patients who were treated with NMES walked an average of 39.3 metres further than patients who received no NMES treatment (95%-CI = 16.3 to 62.2; *n* = 72). A difference of 30 metres is internationally considered to be clinically relevant (Holland 2015).

The effect of NMES on functional exercise capacity was measured in three studies with endurance tests; the Constant Capacity Cycling Test and the Endurance Shuttle Walk Test (ESWT). Patients who received NMES treatment also showed a major improvement in these tests; they lasted an average of 3.62 minutes longer (95%-CI = 2.33 to 4.91; *n* = 55). Bourjeily-Habr (2002) also shows a significant effect of NMES on the physical capacity, which is measured here with the Incremental Shuttle Walk Test (ISWT; *n* = 18; effect size unknown: no data available). See the forest plot.

The evidentiary value for the functional exercise capacity was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision). The evidentiary value is therefore *low*.

***Forest plot of treatment with NMES (standalone) in patients with stable COPD: functional exercise capacity***

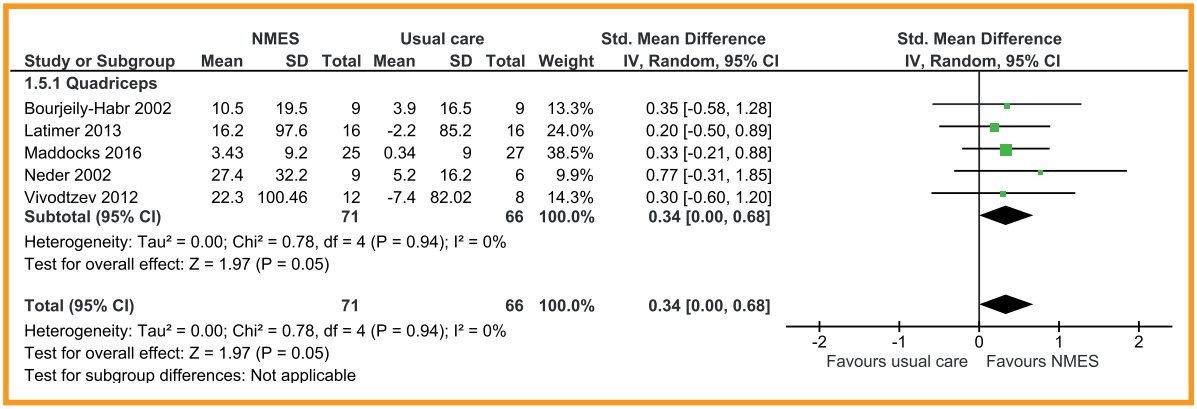



***Peripheral muscle strength***

Five studies found a small increase in the strength of the quadriceps muscles after NMES treatment (SMD = 0.34; 95%-CI = 0.00 to 0.68; *n* = 137). Bourjeily-Habr (2002) also shows increased strength of the hamstrings. See the forest plot. The evidentiary value for the peripheral muscle strength was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision).

The evidentiary value is therefore *low*.

***Forest plot of treatment with NMES (standalone) in patients with stable COPD: peripheral muscle strength***




***Mortality***

Mortality was reported in 12 studies. In these studies, no risk difference (RD) was found between NMES and usual care (5 studies; *n* = 131; RD = -0.02; 95%-CI = -0.08 to 0.05).

The evidentiary value for the serious adverse event mortality was lowered by one level given the small number of patients (imprecision). The evidentiary value is therefore *moderate*.

***Adverse events***
The five studies on adverse events related to NMES showed no increased risk compared to usual care (RD = −0%; 95%-CI = −0.07 to 0.07; *n* = 139).
The evidentiary value for the adverse events related to the intervention was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision). The evidentiary value is therefore *very low*.

An overview of the effects and the evidentiary value for all outcomes is provided in the following table.

***GRADE evidence profile of treatment with NMES without exercise therapy (standalone) compared to usual care in patients with stable COPD***

| **RCTs (*n*)** | **Quality assessment** | | | | | **Summary of results** | | | **GRADE** |
|---|---|---|---|---|---|---|---|---|---|
| | Study design and execution (RoB) | Inconsistency | Indirectness | Imprecision | Publication bias | Patients (*n*) | | Effect size (95%-CI) | |
| | | | | | | I | C | | |
| **Quality of life** | | | | | | | | | |
| 2 | 1 level | none | none | 1 level | none | 36 | 36 | SGRQ: MD = −4.12 (−12.60 to 4.35) points | low |
| **Physical functioning** | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - |
| **Dyspnoea** | | | | | | | | | |
| 3 | 1 level | 1 level | none | 1 level | none | 32 | 23 | Borg Scale, after completion of the exercise test: MD = −1.03 (−2.13 to 0.06) points | very low |
| **Functional exercise capacity** | | | | | | | | | |
| 3 | 1 level | none | none | 1 level | none | 36 | 36 | 6MWT: MD = 39,26 (16,31 tot 62,22) m | low |
| 3 | 1 level | none | none | 1 level | none | 32 | 23 | endurance tests (constant load cycle test and ESWT): MD = 3.62 (2.33 to 4.91) min. | low |
| **Peripheral muscle strength** | | | | | | | | | |
| 5 | 1 level | none | none | 1 level | none | 71 | 66 | quadriceps muscles: SMD = 0.34 (0.00 to 0.68) | low |
| **Mortality** | | | | | | | | | |
| 5 | none | none | none | 1 level | none | 68 | 63 | RD = 2% (−8 to +5) | moderate |
| **Adverse events** | | | | | | | | | |
| 5 | 1 level | none | none | 1 level | none | 72 | 67 | RD = 0% (−7 to +7) | low |

I = intervention group; C = control group. 6MWT: Six Minute Walk Test; ESWT = Endurance Shuttle Walk Test; m = metre(s); MD = mean difference; RD = risk difference; SGRQ = St. George's Respiratory Questionnaire.

**NMES in combination with exercise therapy (add-on) compared to exercise therapy alone in patients with stable COPD**

*Quality of life*

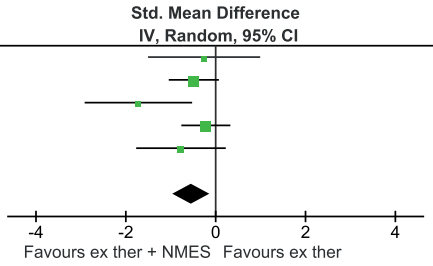
The effect of NMES in combination with exercise therapy on the quality of life was reported in five studies (Akinlabi 2013; Bonnevie 2018; Dang 2011; Tardif 2015; Vivodtzev 2006). The SGRQ (3 studies), the Chronic Respiratory Disease Questionnaire (CRDQ) and the Maugeri Respiratory Failure (MRF-28) were used in the studies. The meta-analysis shows a moderate to large effect (SMD = −0.55; 95%-CI = −0.96 to −0.13; *n* = 146) in favour of NMES with exercise therapy compared to exercise therapy alone. See the forest plot.

The evidentiary value for the quality of life was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision). The evidentiary value is therefore *low*.

*Forest plot of treatment with NMES (add-on) in patients with stable COPD: Quality of life*

| | Exercise therapy + NMES | | | Exercise therapy | | | | Std. Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI |
| Akinlabi 2013 | 11 | 11 | 5 | 14 | 10 | 5 | 9.8% | -0.26 [-1.51, 0.99] |
| Bonnevie 2018 | -5 | 2 | 27 | -3.7 | 3.2 | 24 | 32.3% | -0.49 [-1.04, 0.07] |
| Dang 2011 | -24 | 13 | 8 | -5 | 7 | 8 | 10.5% | -1.72 [-2.92, -0.52] |
| Tardif 2015 | -5 | 12 | 27 | -2 | 15 | 25 | 33.1% | -0.22 [-0.76, 0.33] |
| Vivodtzev 2006 | -15 | 13 | 9 | -1 | 21 | 8 | 14.3% | -0.77 [-1.77, 0.22] |
| **Total (95% CI)** | | | **76** | | | **70** | **100.0%** | **-0.55 [-0.96, -0.13]** |

Heterogeneity: Tau² = 0.06; Chi² = 5.45, df = 4 (P = 0.24); I² = 27%
Test for overall effect: Z = 2.56 (P = 0.01)




*Physical functioning*

Effects of NMES on physical functioning were not investigated in any of the included studies.

*Dyspnoea*

The degree of dyspnoea in daily life was investigated in two studies (Dang 2011; Vivodtzev 2006). However, both studies reported insufficient data for a meta-analysis. In the study by Dang (2011) it was unclear if there was a difference between the improvement of the intervention group and that of the control group. The difference in the study by Vivodtzev (2006) was on the border of significance (*p* = 0.05).

The effects of NMES on dyspnoea immediately after the end of a symptom-limited exercise test was investigated in three studies with the Borg Scale (Bonnevie 2018; Tasdemir 2015; Vivodtzev 2006). Patients in de NMES group scored 0.22 points lower on this scale than patients in the control group (95%-CI = −0.83 to 0.40; *n* = 95); a slight effect.

The evidentiary value for (functional) exercise capacity was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision). The evidentiary value is therefore *low*. See the forest plot.

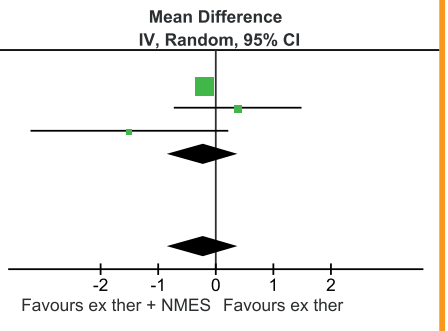
*Forest plot of treatment with NMES (add-on) in patients with stable COPD: dyspnoea*

| | Exercise therapy + NMES | | | Exercise therapy | | | | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI |
| **2.3.2 After an exercise test** | | | | | | | | |
| Bonnevie 2018 | -0.4 | 0.15 | 27 | -0.2 | 0.15 | 24 | 68.0% | -0.20 [-0.28, -0.12] |
| Tasdemir 2015 | -0.25 | 0.9 | 13 | -0.63 | 1.9 | 14 | 21.2% | 0.38 [-0.73, 1.49] |
| Vivodtzev 2006 | -0.5 | 2.3 | 9 | 1 | 1.2 | 8 | 10.8% | -1.50 [-3.22, 0.22] |
| **Subtotal (95% CI)** | | | **49** | | | **46** | **100.0%** | **-0.22 [-0.83, 0.40]** |

Heterogeneity: Tau² = 0.14; Chi² = 3.25, df = 2 (P = 0.20); I² = 38%
Test for overall effect: Z = 0.69 (P = 0.49)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Total (95% CI)** | | | **49** | | | **46** | **100.0%** | **-0.22 [-0.83, 0.40]** |

Heterogeneity: Tau² = 0.14; Chi² = 3.25, df = 2 (P = 0.20); I² = 38%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



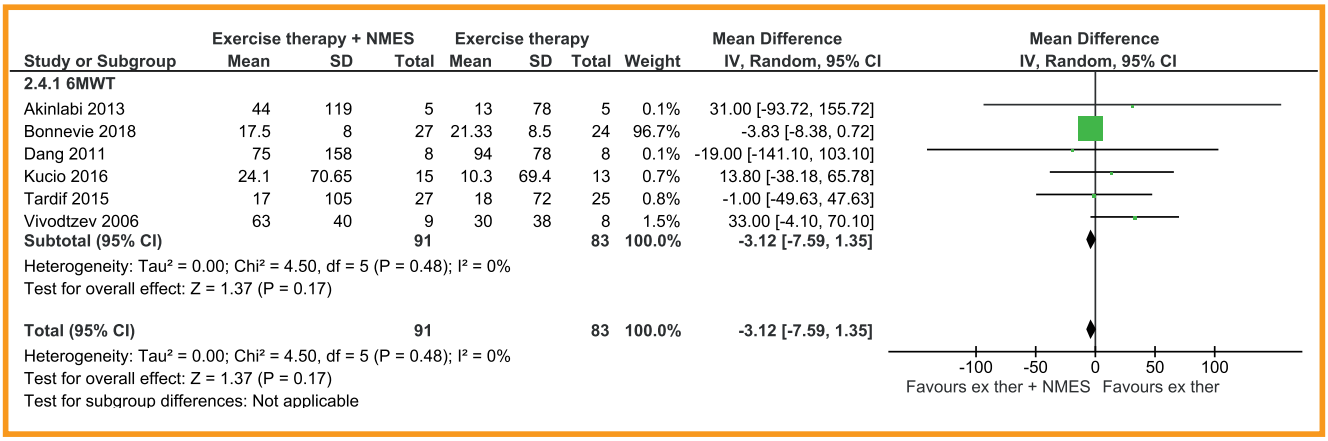
*Functional exercise capacity*

In combination with exercise therapy, NMES has no effect (even a very small negative effect) on the functional exercise capacity compared to regular exercise therapy without NMES. In six studies, patients who received exercise therapy plus NMES walked on average three metres less than patients who received exercise therapy without NMES (95%-CI = -7.6 to 1.4; *n* = 174). The ISWT also showed no significant effects of exercise therapy plus NMES on exercise capacity, but the ESWT did (Tasdemir 2015; insufficient data reported for calculating the effect size and/or inclusion in a meta-analysis). See the forest plot.

The evidentiary value for functional exercise capacity was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision).

The evidentiary value is therefore *low*.

*Forest plot of treatment with NMES (add-on) in patients with stable COPD: functional exercise capacity*

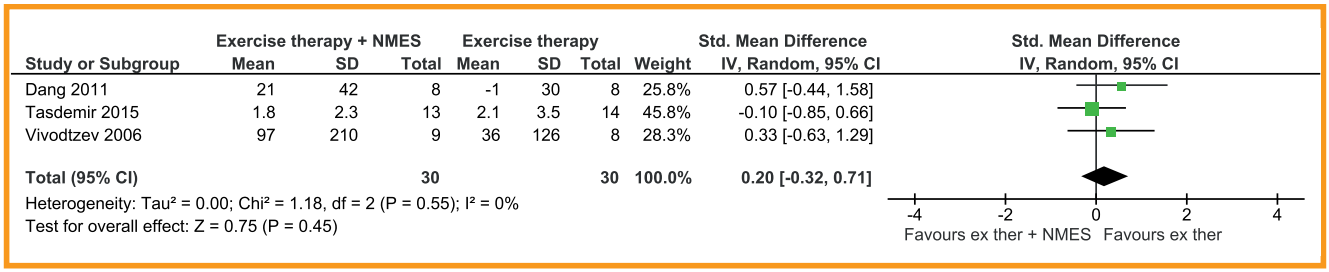



*Peripheral muscle strength*

Three studies (Dang 2011; Tasdemir 2015; Vivodtzev 2006) reported a small increase in the strength of the quadriceps muscles (SMD = 0.20; 95%-CI = -0.32 to 0.71; *n* = 60). See the forest plot.

The evidentiary value for the effect on peripheral muscle strength was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision). The evidentiary value is therefore *low*.

*Forest plot of treatment with NMES (add-on) in patients with stable COPD: peripheral muscle strength*

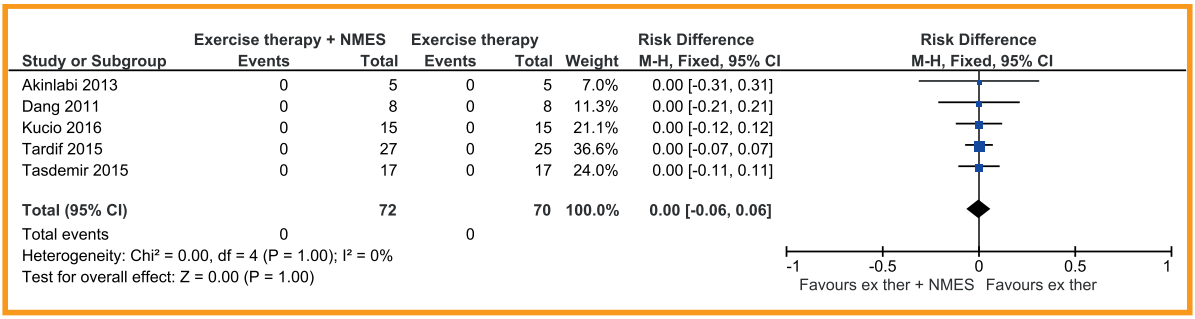



*Mortality*

There may be no risk difference in mortality between exercise therapy with and without NMES. No patients died in any of the five studies that reported data about mortality (RD = 0.00; 95%-CI = -0.06 to 0.06; *n* = 142). See the forest plot.

The evidentiary value for the mortality outcome measure was lowered by one level given the small number of patients (imprecision). The evidentiary value is therefore *moderate*.

*Forest plot of treatment with NMES (add-on) in patients with stable COPD: mortality*




*Adverse events*

NMES may not increase the risk of adverse events in exercise therapy with NMES compared to exercise therapy without NMES (six studies; *n* = 144; RD = 0.0; 95%-CI = −0.05 to 0.05).

The evidentiary value for the adverse events related to the intervention was lowered by two levels given the limitations of the study design and execution (including blinding) and the small number of patients (imprecision). The evidentiary value is therefore *low*.

An overview of the effects and the evidentiary value for all outcomes is provided in the following table.

*GRADE evidence profile of the results of NMES in combination with exercise therapy (add-on) compared to exercise therapy alone in patients with stable COPD*

| RCTs (*n*) | Quality assessment | | | | | Summary of results | | | GRADE |
|---|---|---|---|---|---|---|---|---|---|
| | Study design and execution (RoB) | Inconsistency | Indirectness | Imprecision | Publication bias | Patients (*n*) | | Effect size (95%-CI) | |
| | | | | | | I | C | | |
| **Quality of life** | | | | | | | | | |
| 5 | 1 level | none | none | 1 level | none | 76 | 70 | SMD = −0,55 (−0,96 tot −0,13) | low |
| **Physical functioning** | | | | | | | | | |
| 2 | 1 level | none | none | 1 level | none | 22 | 22 | time to transfer bed-chair: MD = −4.98 (−8.55) | low |
| **Dyspnoea** | | | | | | | | | |
| 2 | 1 level | none | none | 1 level | none | 22 | 22 | Borg Scale, immediately after the exercise test: MD = −0.22 (−.83 to 0.40) points | low |
| **Functional exercise capacity** | | | | | | | | | |
| 7 | 1 level | none | none | 1 level | none | 100 | 89 | 6MWT: MD = −3.12 (−7.59 to 1.35) m | low |
| **Peripheral muscle strength** | | | | | | | | | |
| 3 | 1 level | none | none | 1 level | none | 30 | 30 | SMD = 0.20 (−0.32 to 0.71) | low |
| **Mortality** | | | | | | | | | |
| 5 | none | none | none | 1 level | none | 72 | 70 | RD = 0% (−6 to +6) | moderate |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Adverse events** | | | | | | | | | |
| 4 | 1 level | none | none | 1 level | none | 53 | 52 | RD = 0.0 (−0.06 to 0.06) | low |

I = intervention group; C = control group. 6MWT = Six Minute Walk Test; MD = mean difference; Med.= median; RD = risk difference. SMD = standardized mean difference.

**Considerations**

The considerations and recommendations stem from the deliberations held in the guideline panel based on the evidence-to-decision forms. See appendix C.3.5.

The considerations concerned:

**Desirable effects** For patients with stable COPD who are able to engage in physical training, application of NMES in combination with physical training (add-on) is barely of added value compared to exercise therapy without NMES. Given these results, treatment with NMES does not add value to physical training in patients with stable COPD and treatment with NMES does not appear to be useful for these patients. When patients with stable COPD do not receive any physical training, administration of NMES may improve the exercise capacity and the peripheral muscle strength compared to usual care, for example. These are patients who are not able to engage in physical training, for example because they are bed-ridden and/or experiencing a serious exacerbation. Patients may also not be able to engage in physical training due to orthopaedic problems. Although there are no known studies on the effects of NMES in patients with COPD and orthopaedic problems, there are literature studies that show positive effects of NMES in this patient group, but without COPD (Gate wood 2017; Herzig 2015). For COPD patients who are hospitalised due to an exacerbation, the combination of NMES and mobilisation exercises results in a significant to very significant improvement of physical functio ning, dyspnoea, exercise capacity and peripheral muscle strength.

**Undesirable effects** Treatment with NMES appears to be safe; no situations were found that result in an incre ased risk of mortality or adverse events related to the intervention.

**Balance between desirable and undesirable effects** The desirable effects of NMES in COPD patients likely outweigh the undesirable effects. NMES always leads to desirable effects in patients who were hospitalised due to an exacerbation and in patients with stable COPD without physical training (standalone). What's more, there is no increased risk of undesirable effects. For patients with stable COPD who are able to engage in physical training, there appear to be hardly any desirable effects of NMES; as such, NMES does not outweigh the pos sible undesirable effects for this group.

**Value of the desirable effects** For patients who are hospitalised due to an exacerbation, NMES is of great value for the physical functioning (transfer from bed to chair), dyspnoea and exercise capacity. Even when patients with stable COPD are unable to perform physical training, NMES can have a positive effect on decon ditioning.

**Variation in the value of the desirable effects** The value that patients attribute to NMES will vary greatly. The effects of NMES are of great value for hospital patients, but for patients who are able to train their endu rance themselves the value of NMES is very low.

**Required resources (costs)** The costs of NMES for the therapist consist of acquiring the NMES equipment; these costs amount to about EUR 600 for a four-channel muscle stimulation device. There are no additional costs associated for NMES treatment for patients when they have been hospitalised or have been admitted to a hospital or a rehabilitation facility (the treatment is included and is reimbursed by the basic healthcare insurance). For patients without indication for hospital treatment or pulmonary rehabilitation, the costs of NMES treatment fall under the therapist's regular treatment.

**Variation in required resources (costs)** The variation in required resources is high. The equipment is usually present in hospitals and pulmonary rehabilitation facilities. However, the equipment is not a part of the standard equipment of primary care practices and is hence not always available. If NMES treatment is indicated and the practice does not have the right equipment, then the patient is referred to a practice that can admi nister NMES treatment.

**Cost-effectiveness** Studies on cost-effectiveness were not found. The cost-effectiveness of NMES is estima ted to be favourable. Given the positive effects of physical functioning, NMES may shorten the length of hospi tal stay of hospital patients. The cost-effectiveness of NMES treatment appears to be favourable in primary care practice as well. Hospitalisation may be avoided when treating an exacerbation and preventing further decon ditioning.

**Acceptability** Patients do feel the muscle contraction but do not experience pain from the neuromuscular electrical stimulation.

**Feasibility** Implementing NMES in daily practice is likely feasible. The NMES equipment is usually available in hospitals and pulmonary rehabilitation facilities. Take into account the availability of NMES equipment when providing treatment in a primary care practice and refer the patient to a practice that has NMES equipment.

### NMES in combination with mobilisation in patients who are hospitalised with a COPD exacerbation (IC or HC)

***Quality of life***

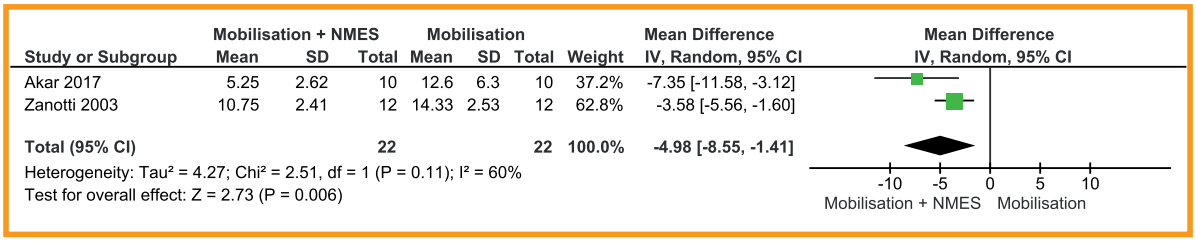
The effect of NMES on quality of life has not been reported.

***Physical functioning***

Two studies in IC patients investigated the time to sitting out of bed (Akar 2017; Zanotti 2003). These studies show a very large effect of NMES in combination with mobilisation on physical functioning; patients in the intervention group could sit out of bed on average five days earlier (95%-CI = -8.6 to -1.4; *n* = 44). See the forest plot.

The evidentiary value for physical functioning was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision). The evidentiary value is therefore *low*.

***Forest plot for treatment with NMES in patients who were admitted to hospital (IC or HC) with a COPD exacerbation: physical functioning; time to first transfer from bed to chair (in days)***




***Dyspnoea***

Symptoms of dyspnoea as measured with the Medical Research Council Dyspnoea questionnaire (MRC) decreased by one point more after treatment with NMES than after placebo treatment (Abdellaoui 2011). The evidentiary value for dyspnoea was lowered by three levels given the limitations of the study design and execution (one level) and the small number of patients (imprecision; two levels). The evidentiary value is therefore *very low*.

***Functional exercise capacity***

NMES may results in a large, clinically relevant improvement of the functional exercise capacity. In the study by Abdellaoui (2011), patients who received mobilisation with NMES walked on average 164.0 (± 68.2) metres and patient who received mobilisation with placebo NMES walked on average 72 (± 68.5) metres. At 92.0 metres, the difference in walking distance was very large (95%-CI = 21.36 to 162.64; *n* = 15). The evidentiary value for dyspnoea was lowered by three levels given the limitations of the study design and execution (1 level) and the small number of patients (imprecision; two levels). The evidentiary value is therefore *very low*.

***Peripheral muscle strength***

Zanotti (2003) shows a very large effect of NMES on muscle strength. Measured using an MRC scale of 0 (no visible or tangible contraction) to 5 (normal strength), mobilisation with NMES resulted in greater improvement of the muscle strength score (average score= 2.16 ±1.02) than mobilisation without NMES (score = 1.25 ±0.75; SMD = 1.20; 95%-CI = 0.32 to 2.08).

Abdelloui (2011) also shows a greater increase of muscle strength of the quadriceps muscles after mobilisation with NMES (median MVC = 10; IQR = 4.7-11.5 kg) than after mobilisation with placebo NMES (median MVC = 3; IQR = 1-5 kg; *p* = 0.02).

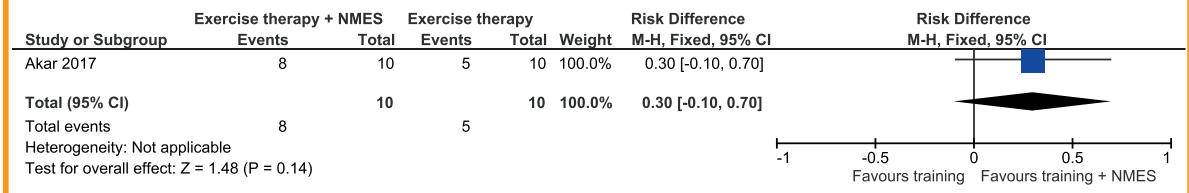
The evidentiary value for dyspnoea was lowered by two levels given the limitations of the study design and execution (1 level) and the small number of patients (imprecision; one level). The evidentiary value is therefore *low*.

***Length of hospital stay***

One study reports information about the length of hospital stay. This study by Akar (2017) shows a 30% (95%-CI = -0.10 to 0.70) greater chance of discharge from the ICU within four weeks after treatment with mobilisation plus NMES (8 of 10 patients were discharged from the ICU within 4 weeks) compared to patients who only received mobilisation (5 of 10 patients). See the forest plot.

The evidentiary value for length of hospital stay was lowered by two levels given the limitations of the study design and execution (1 level) and the very small number of patients (imprecision; two levels). The evidentiary value is therefore *very low*.

***Forest plot for treatment with NMES in patients who were admitted to the hospital (IC or HC) with a COPD exacerbation: length of hospital stay; discharge from ICU within four weeks***




***Mortality***

Treatment with NMES may not increase the risk of death (Zanotti 2003; Abdellaoui 2011).

The evidentiary value for dyspnoea was lowered by one level given the small number of patients (imprecision) and is therefore *moderate*.

***Adverse events***

NMES may not increase the risk of adverse events (Abdellaoui 2011).

The evidentiary value for adverse events was lowered by three levels given the limitations of the study design and execution (1 level) and the small number of patients (imprecision; two levels). The evidentiary value is therefore *very low*.

An overview of the effects and the evidentiary value for all outcomes is provided in the following table.

***GRADE evidence profile for NMES in combination with mobilisation (add-on) compared to mobilisation alone in COPD patients admitted to the IC or HC department of the hospital***

| **RCTs (*n*)** | **Quality assessment** | | | | | **Summary of results** | | | **GRADE** |
|---|---|---|---|---|---|---|---|---|---|
| | Study design and execution (RoB) | Inconsistency | Indirectness | Imprecision | Publication bias | Patients (*n*) | | Effect size (95%-CI) | |
| | | | | | | I | C | | |
| **Quality of life** | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - |
| **Physical functioning** | | | | | | | | | |
| 2 | 1 level | none | none | 1 level | none | 22 | 22 | time to transfer bed-chair: MD = -4.98 (-8.55 to -1.41) days | low |
| **Dyspnoea** | | | | | | | | | |
| 1 | 1 level | none | none | 2 level | none | 9 | 6 | MRC: MD = 1 point | very low |
| **Functional exercise capacity** | | | | | | | | | |
| 1 | 1 level | none | none | 2 levels | none | 9 | 6 | 6MWT: MD = 92 (21.4 to 162.6) m | very low |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Peripheral muscle strength** | | | | | | | | | |
| 2 | 1 level | none | none | 1 level | none | 21 | 18 | Zanotti 2003: score, SMD = 1.20 (0.32 to 2.08)<br>Abdellaoui 2011: MVC of the quadriceps muscles NMES: med. (IQR) = 10 (4.7 to 11.5 kg); placebo: med. (IQR) = 3; 1–5 kg; $p$ = 0.02 | low |
| **Length of hospital stay, discharge from the IC within 4 weeks** | | | | | | | | | |
| 1 | 1 level | none | none | 2 levels | none | 10 | 10 | Akar 2017: RD = 0.30 (−0.10 to 0.70) | very low |
| **Mortality** | | | | | | | | | |
| 2 | none | none | none | 1 level | none | 21 | 18 | RD = 0 | moderate |
| **Adverse events** | | | | | | | | | |
| 1 | 1 level | none | none | 2 levels | none | 9 | 6 | RD= 0 | very low |

I = intervention group; C = control group. 6MWT = Six Minute Walk Test; IQR= Interquartile Range; MD = Mean Difference; Med. = median; MRC = Medical Research Council; MVC = Maximal Voluntary Contraction; NMES = Neuromuscular Electrical Stimulation; RD = Risk Difference; SMD = Standardized Mean Difference.

### Literature on administration of NMES

To answer the clinical question* about the manner of administering NMES, it was decided in consultation with the guideline panel and the review panel not to conduct a systematic review for pragmatic reasons. The literature about this topic was collected in a non-systematic manner and is mentioned in the literature list below.

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* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

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## Note C.4 Interventions aimed at the respiratory system

### Note C.4.1 Respiratory muscle training

#### Clinical question

The clinical question on respiratory muscle training is divided into two sub-questions:

- **What is the value of inspiratory muscle training for COPD patients?**
- **How (FITT) should inspiratory muscle training be administered to COPD patients?**

#### Literature about the value of inspiratory muscle training

To answer the first clinical question* about the value of the inspiratory muscle training, the conclusions of the systematic review of Beaumont (2018) were adopted.

**Outcome measures**

Quality of life, physical capacity, and dyspnoea are listed as patient-relevant outcome measures crucial to the decision-making process. The occurrence of adverse events is listed as a patient-relevant and important outcome measure for the decision-making process.

**Search and selection**

Because a very recent systematic review (SR) was already identified (Beaumont 2018) that is aligned with this clinical question, a decision was made not to perform an additional systematic review. The results of the systematic review of Beaumont (2018) were adopted.

The SR of Beaumont was selected based on the selection criteria in the following table.

| *Selection criteria* | |
|---|---|
| Type of studies | SRs |
| Type of patients | adults with COPD |
| Type of interventions | any form of inspiratory muscle training |
| Type of comparisons | as standalone therapy compared to no therapy, or as a supplement to physical training compared to physical training alone |
| Type of outcomes (desirable and undesirable effects) | • crucial outcome measures: quality of life, physical capacity and dyspnoea<br>• 'important outcome measures': adverse events |
| Type of timeline | immediately after the intervention |
| Other | availability of the complete text |

**Literature summary**

*Description of studies*

In the Beaumont (2018) SR, 43 studies are included, with a total of 1,427 patients with COPD.
In the SR, inspiratory muscle training (IMT) and no IMT were compared as standalone intervention and as additional intervention (add-on) in addition to exercise training. IMT was an additional type of training in four studies. In the other studies, IMT was investigated as a standalone intervention.
An inclusion criterion within this review was the use of a threshold device. Both patients in a stable phase as well as patients with an exacerbation could be included.

* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

*Individual study quality*
The individual study quality was assessed by Beaumont (2018) using the Physiotherapy Evidence Database (PEDro) scale (RCTs) and the Downs and Black tool (observational studies). The methodological quality of the RCTs varied from 3 to 8/10 (PEDro score) and the quality of the observational studies varied from 1151 to 1236 (Downs and Black score).

**Results and evidentiary value**

*Functional physical capacity*
The effect pf respiratory muscle training was investigated in 33 studies on functional physical capacity. In 22 of these 33 studies the effect was measured using the Six Minute Walk Test (6MWT). The meta-analysis from the SR (Beaumont 2018) shows a moderate, clinically relevant difference in favour of respiratory muscle training (MD 42.68 m; 95%-CI = 16.90 to 68.47; *n* = 615). The functional physical capacity was measured using the 12MWT in five studies and the Incremental Shuttle Walk Test (ISWT) in three studies. The meta-analysis also showed a small, clinically relevant improvement with these measurement instruments (ISWT: 53.96 (95%-CI = -32.19-140.11); 12MWT: 114.55 (95%-CI = -89.54 to 318.63).
The evidentiary value for the effect of respiratory muscle training on functional physical capacity was lowered by two levels given the limitations of the study design and execution. The evidentiary value is therefore low.

*Dyspnoea*
A total of 23 studies investigated the effect of respiratory muscle training on dyspnoea. Measured with the Borg Scale or the Visual Analogue Scale (VAS), the meta-analysis from the SR (Beaumont 2018) does not show a difference between the two groups (MD = -0.52; 95%-CI = -1.09 to 0.05). Measured with the Baseline-Transition Dyspnea Index (BDI-TDI), the meta-analysis shows a large difference in favour of respiratory muscle training (MD 2.30; 95%-CI = 1.67 to 2.93).
The evidentiary value for the effect of respiratory muscle training on dyspnoea was lowered by two levels given the limitations of the study design and execution. The evidentiary value is therefore low.

*Quality of life*
A total of nine studies investigated the effect of respiratory muscle training on quality of life. Measured with the St. George's Respiratory Questionnaire (SGRQ) (5 studies), the meta-analysis from the SR (Beaumont 2018) does not show a difference between the group that did and the group that did not receive respiratory muscle training (MD = -2.40; 95%-CI = -4.89 to 0.09).
The evidentiary value for the effect of respiratory muscle training on functional physical capacity was lowered by two levels given the limitations of the study design and execution. The evidentiary value is therefore low.

*Undesirable effects*
No statements are made about possible undesirable effects in the Beaumont SR.

**Considerations**
The considerations and recommendations stem from the deliberations held in the guideline panel based on the evidence-to-decision forms. See appendix C.4.1

The considerations concerned:
**Desirable effects** No effect was found on the quality of life outcome measure. However, respiratory muscle training does lead to a moderate improvement of physical capacity and possibly to a significant decrease of dyspnoea (depending on the measurement instrument) compared to no therapy. However, no difference in effect was found on the outcome measures physical capacity and dyspnoea between groups where respiratory muscle training is added to physical training as an additional intervention. No studies were identified for the differences on the quality of life outcome measure.
**Undesirable effects** These were not reported.
**Quality of the desirable effects**The evidentiary value of the listed effects is low.
**Balance between desirable effects and undesirable effects** Undesirable effects are not known.
**Value of the desirable effects** The patients are not expected to attribute a lot of value to the desirable effects.
**Variation in the value of the desirable effects** A reasonably large variation in the value that patients attribute to the training is expected. This might have to do with the motivation for following a training programme.
**Required resources (costs)** For respiratory muscle training, a device must be acquired that costs several tens of euros. For hygienic reasons, it is recommended that patients purchase this device themselves, but the device is not reimbursed by health insurance.

**Variation in required resources (costs)** Whether or not a patient has the financial resources for such a device will differ per patient.
**Cost-effectiveness** Not reported.
**Acceptability** There are no reasons to assume that implementing this intervention is not acceptable.
**Feasibility** There are no reasons to assume that implementing this intervention is not feasible.

Given the effects that respiratory muscle training has on physical capacity and dyspnoea compared to no therapy, a conditional recommendation for the intervention was decided on.
This means that the intervention is recommended if:

- a patient has dyspnoea and if the goal is to decrease this dyspnoea and/or severe dyspnoea makes endurance/interval training virtually impossible and;
- the patient has sufficient motivation and skills to independently perform the respiratory muscle training (after instruction) and is willing to acquire the required equipment.

#### Literature Manner of administering (FITT) inspiratory muscle training

To answer the clinical question* about the manner of administering inspiratory muscle training, it was decided in consultation with the guideline panel and the review panel not to conduct a systematic review. The literature about this topic was collected in a non-systematic manner and is mentioned in the literature list below.

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### Note C.4.2 Breathing techniques

#### Clinical question

**What is the value of breathing techniques for COPD patients?**

#### Literature

To answer the clinical question*, a systematic analysis of the literature was carried out according to the following review question:

- 'What are the favourable (effectiveness) and adverse (side) effects of breathing techniques on dys pnoea, physical capacity and quality of life of COPD patients?'

* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

**Outcome measures**

Dyspnoea, physical capacity, quality of life and undesirable effects are listed as patient-relevant outcome measures crucial and important to the decision-making process.

The 'Medical Research Council' (MRC) Dyspnoea Scale is the preferred scale for the dyspnoea outcome measure, and otherwise the Borg Scale. The Six Minute Walk Test (6MWT) is the preferred test for the physical capacity outcome measure, and the total score of the St. George's Respiratory Questionnaire (SGRQ) for the quality of life outcome measure. With respect to the quality of life, the score on the central apnoea index (CAI) was also separately given for the combined breathing techniques, because it was not known whether this scale could be pooled with the other measurement instruments because the direction of the scale and the scale distribution were unknown.

**Search and selection**

*Search*

The systematic review (SR) of Holland (2012) was used to answer this clinical question. The review was then updated. The systematic search was repeated on 3 August 2018 in the PubMed, EMBASE, Web of Science, Cochrane Library, CENTRAL, EmCare, PsycINFO, ERIC and PEDro databases. Relevant search terms were used to search for new randomised controlled studies published in English or Dutch starting in 2012 (year of Holland 2012 search).

*Literature selection*

All 16 RCTs from the Holland (2012) review were tested according to the selection criteria for this clinical question. Then eight studies were included in the review. The other eight studies reported no relevant outcome measures. The articles that were excluded based on the complete text and the reason of the exclusion are listed in appendix C.4.2.

The additional search yielded a total of 1,828 unique hits. The studies found were selected based on the following selection criteria: it concerns a randomized controlled parallel-group trial (RCT), the study was conducted in COPD patients, the intervention entails breathing techniques and reports on the dyspnoea, quality of life and/or physical capacity outcome measures.

After selection based on title and abstract, the complete text of 15 studies was consulted. Then 12 studies were excluded based on the complete text. The guideline panel also proposed various articles during the process that were all controlled but did not comply with the inclusion criteria (see appendix C.4.2 for the reason for the exclusion). Some studies were included in the considerations as additional information.

The three studies that were selected (Borge 2014; Valenza 2016; Xi 2015) investigated ventilation feedback (Borge 2014) or combinations of various breathing techniques (Valenza 2014; Xi 2015) and compared the intervention with usual care or a group that received comparable therapy without breathing techniques. The studies included patients with moderate to severe COPD (Borge 2015; Xi 2015) or patients who had just been hospitalised with an acute exacerbation (Valenza 2016). The three studies were added to the Holland (2012) SR.

**Literature summary**

*Description of studies*

The 11 included studies describe the effects of four respiratory interventions: pursed lip breathing (PLB, 4 studies, total of 130 patients with stable COPD), diaphragmatic breathing (1 study, 20 patients with stable COPD), ventilation feedback (3 studies, 281 patients with stable COPD) and combined/other breathing techniques (3 studies, 265 patients with stable COPD).

The Holland (2012) study did not always report in which conditions (at rest or during activities) or in which setting the breathing technique was applied. In the studies, the breathing technique was compared to no breathing technique or an exercise programme plus the breathing technique was compared with the exercise programme alone.

In the three studies on ventilation feedback (also biofeedback), supervised deep breathing was applied at rest, with ventilation feedback during exercise and ventilation feedback in an unknown setting.

Combined/other respiratory interventions often entail a combination of breathing techniques such as PLB, active expiration, abdominal respiration or diaphragmatic breathing, and controlled breathing in combination with exercises/activities.

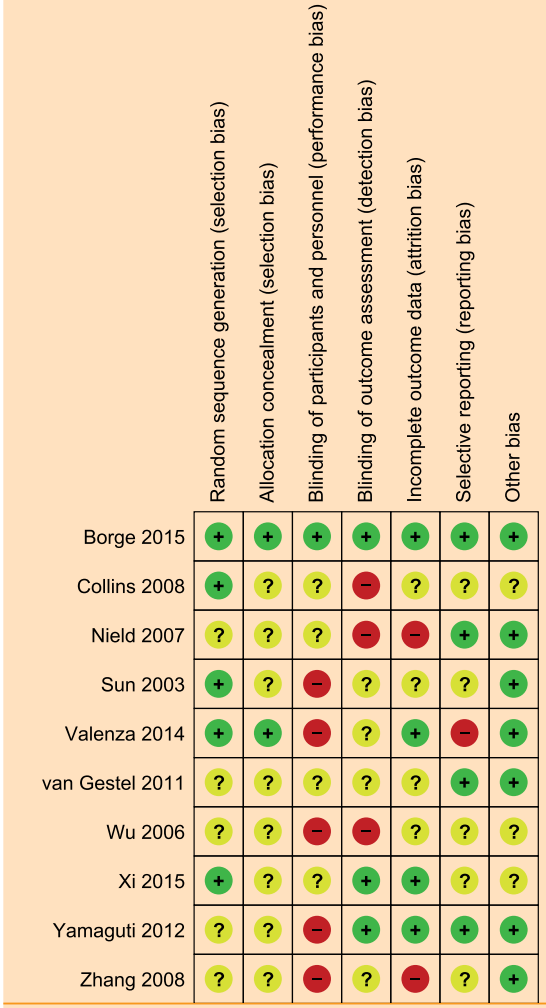
A detailed overview of the included studies is available online as 'Appendix Evidence Tables'.

*Individual study quality*

The design and execution of the individual studies ('risk of bias'; RoB) was assessed with the help of the

Cochrane Risk-of-Bias tool. This literature review on breathing techniques entails a total of 11 studies; eight studies from the Holland 2012 review and three recent studies from the update. Of these 11 studies, the results on the dyspnoea, physical capacity and quality of life (QoL) outcome measures were extracted. The assessment of the individual study quality of the 11 included studies is provided in the following table.

***Risk of bias: Breathing techniques***




\+ = yes; – = no; ? = unclear

**Results and evidentiary value**

The results and evidentiary value of the following are described below:

- pursed lip breathing (PLB);
- diaphragmatic breathing;
- ventilation feedback;
- combined respiratory interventions.

**Pursed lip breathing (PLB)**

***Dyspnoea***

When comparing PLB versus no respiratory training, dyspnoea is measured using the modified Medical Research Council Dyspnoea questionnaire (mMRC) and the California San Diego Shortness of Breath Questionnaire (CSDSBQ). Immediately after the intervention, two studies (Nield 2007; Zhang 2008) in 49 patients

concluded that for COPD patients, PLB has a moderate effect on dyspnoea compared to no respiratory training (SMD = -0.75; 95%-CI = -1.34 to -0.17).
The evidentiary value for the dyspnoea outcome measure was lowered by two levels given the limitations of the study design and execution (RoB) and by one level given the small number of patients (imprecision) for the studies of Nield (2007) and Zhang (2008). The evidentiary value is *very low*.

***Physical capacity***
The 6MWT is used to measure physical capacity when comparing PLB versus no respiratory training. Eight weeks after the intervention, one study (Zhang 2008) in 30 patients concluded that for COPD patients, PLB has a very large effect on physical capacity compared to no respiratory training (SMD = 2.71; 95%-CI = 1.68 to 3.73).
The evidentiary value for the physical capacity outcome measure was lowered by three levels given the limitations of the study design and execution (RoB) and the small number of patients (imprecision) for the Zhang (2008) study. The evidentiary value is *very low*.

***Quality of life***
The quality of life-related dyspnoea was subjectively assessed using the Hirastsuka Scale when comparing PLB versus no respiratory training. Two studies (Wu 2006; Zhang 2008) in 60 patients concluded that according to the Hirastsuka Scale, PLB has a moderate effect on quality of life compared to no respiratory training (SMD = -0.71; 95%-CI = -1.25 to -0.17) for COPD patients. The evidentiary value for the quality of life outcome measure was lowered by three levels given the limitations of the study design and execution (RoB) and the small number of patients (imprecision) for the Wu (2006) and Zhang (2008) studies. The evidentiary value is *very low*.

***Adverse events***
The risk of adverse events is unknown; such incidents have not been reported.
No GRADE assessment of the evidentiary value was performed for adverse effects; there are no studies that report adverse events.

An overview of the effects and the evidentiary value for all outcomes is provided in the following table.

***GRADE evidence profile for pursed lip breathing***

| **RCTs (*n*)** | **Quality assessment** | | | | | **Summary of results** | | | **GRADE** |
|---|---|---|---|---|---|---|---|---|---|
| | Study design and execution | Inconsistency | Indirectness | Imprecision | Publication bias | Patients (*n*) | | Effect size | |
| | | | | | | I | C | SMD (95%-CI) | |
| **Dyspnoea after intervention** | | | | | | | | | |
| 1 | 2 levels[a] | none | none | 1 level[b] | none | 25 | 24 | SMD = -0.75 (95%-CI = -1.34 to -0.17) | very low |
| **Functional/physical capacity** | | | | | | | | | |
| 1 | 2 levels[a] | none | none | 1 level[b] | none | 15 | 15 | SMD = 2.71 (95%-CI = 1.68 to 3.73) | very low |
| **Quality of life** | | | | | | | | | |
| 2 | 2 levels[a] | none | none | 1 level[b] | none | 35 | 25 | Hiratsuka Scale: SMD = -0.71 (95%-CI = -1.25 to -0.17) | very low |

I = intervention group; C = control group. SMD = standardized mean difference.
a Low risk of bias (RoB): randomisation adequate + allocation concealed + intention to treat (ITT); high RoB: < 3 items low risk; moderate RoB: other.
b Dichotomous outcome measure for population (*n* > 300); continuous measure of outcome for population (n > 400)

### PLB considerations

The considerations and recommendations stem from the deliberations held in the guideline panel based on the evidence-to-decision forms. See appendix C.4.2.

The considerations concerned:
**Desirable effects** Application of PLB has a moderate effect on dyspnoea and on the quality of life and a very large effect on physical capacity.
**Undesirable effects** There is a slight undesirable effect. A disruption of the regulation of the breathing is possible but is rarely seen in practice. Sometimes patients think they always need to apply PLB, but by learning how to use it they are then able to apply it at the right times. Dyspnoea is possible if the technique is applied incorrectly. Firstly, patients aren't used to it. By practicing the technique multiple times together with the therapist, COPD patients can learn this technique without experiencing shortness of breath. PLB can work really well for recovery after dyspnoea.
**Quality of desirable effects** The quality of the desirable effects is very low.
**Balance between desirable and undesirable effects** There is a favourable balance between the desirable and undesirable effects. There are barely any undesirable effects and only positive effects of this breathing technique. The favourable effects outweigh the adverse effects.
**Value of desirable effects** A reasonable value is attached to the desirable effects. In principle, patients do PLB automatically, but if they don't, then it is important to learn PLB.
Dyspnoea should always be evaluated with a Borg Scale, because PLB does not always work immediately for everyone and may even be counterproductive. It is often important to make patients who are already unconsciously applying PLB aware of this technique and explain in which other situations they can apply PLB as well. Patients attach a reasonable value to PLB, especially during exercise or for increasing the exercise capacity (Gosselink 2016).
**Variation in value of desirable effects** There is a moderate variation in the value attached to the effects, because many patients already apply PLB. For patients who are not yet applying PLB, more value is attached to the desirable effects.
**Required resources (costs)** There are no extra costs associated with this intervention, and the intervention also does not yield any savings. However, the therapist does require additional training.
**Variation in required resources (costs)** Not reported.
**Cost-effectiveness** No known studies.
**Acceptability** There are no reasons to assume that implementing this intervention is not acceptable.
**Feasibility** There are no reasons to assume that implementing this intervention is not feasible.

PLB is a safe and easy to administer intervention with positive results and has very few or no undesirable effects. There is some variation in the effects, and the quality of the scientific evidence is very low. It is important to teach PLB to patients who are not yet able to apply this technique and to make patients who are already automatically using this technique aware of this and explain in which other situations they can apply PLB as well.

### Diaphragmatic breathing

*Dyspnoea*
Dyspnoea is measured with the mMRC when comparing diaphragmatic breathing versus no respiratory training. Four weeks after the intervention, one study (Yamaguti 2012) with 30 patients (stable COPD with a mean FEV1 of 42%), concluded that diaphragmatic breathing has a *small effect* on dyspnoea in COPD patients compared to no respiratory training (SMD = −0.38; 95%-CI = −1.11 to 0.34).
The evidentiary value for the dyspnoea outcome measure was lowered by two levels given the limitations of the study design and execution (RoB) and the small number of patients (imprecision) for the Yamaguti (2012) study. The evidentiary value is *low*.

*Physical capacity*
Physical capacity is measured with the 6MWT when comparing diaphragmatic breathing versus no respiratory training. Four weeks after the intervention, one study (Yamaguti 2012) in 30 patients concluded that for COPD patients, diaphragmatic breathing has a *moderate to large effect* on physical capacity compared to no respiratory training (SMD = 0.79; 95%-CI = 0.04 to 1.54).
The evidentiary value for the physical capacity outcome measure was lowered by two levels given the limitations of the study design and execution (RoB) and the small number of patients (imprecision) for the Yamaguti (2012) study. The evidentiary value is *low*.

***Quality of life***

The SGRQ is used to measure quality of life when comparing diaphragmatic breathing versus no respiratory training. Four weeks after the intervention, one study (Yamaguti 2012) in 30 patients concluded that for COPD patients, diaphragmatic breathing has a *large effect* on quality of life compared to no respiratory training (SMD = -1.01; 95%-CI = -1.77 to -0.24).

The evidentiary value for the quality of life outcome measure was lowered by two levels given the limitations of the study design and execution (RoB) and the small number of patients (imprecision) for the Yamaguti (2012) study. The evidentiary value is *low*.

***Undesirable effects***

The risk of adverse effects is unknown; these have not been reported.

No GRADE assessment of the evidentiary value was performed for undesirable effects; there are no studies that report adverse effects.

An overview of the effects and the evidentiary value for all outcomes is provided in the following table.

*GRADE evidence profile for diaphragmatic breathing*

| **RCTs (*n*)** | **Quality assessment** | | | | | **Summary of results** | | | **GRADE** |
|---|---|---|---|---|---|---|---|---|---|
| | Study design and execution | Inconsistency | Indirectness | Imprecision | Publication bias | Patients (*n*) | | Effect size | |
| | | | | | | I | C | SMD (95%-CI) | |
| **Dyspnoea after 4 weeks** | | | | | | | | | |
| 1 | 1 level[a] | none | none | 1 level[b] | none | 15 | 15 | SMD = -0,38 (-1,11 tot 0,34) | low |
| **Functional/physical capacity** | | | | | | | | | |
| 1 | 1 level[a] | none | none | 1 level[b] | none | 15 | 15 | SMD = 0,79 (CI = 0,04 tot 1,54) | low |
| **Quality of life** | | | | | | | | | |
| 1 | 1 level[a] | none | none | 1 level[b] | none | 15 | 15 | SMD = -1,01 (-1,77 tot -0,24) | low |

I = intervention group; C = control group. SMD = standardized mean difference; I = intervention group; C = control group.
a Low risk of bias (RoB): randomisation adequate + allocation concealed + intention to treat (ITT); high RoB: < 3 items low risk; moderate RoB: other.
b Dichotomous outcome measure for population (*n* > 300); continuous measure of outcome for population (*n* > 400)

### Considerations for diaphragmatic breathing

The considerations and recommendations stem from the deliberations held in the guideline panel based on the evidence-to-decision forms. See appendix C.4.2.

The considerations concerned:

**Desirable effects** The literature shows various positive effects (small, moderate and large) on the three out come measures.

**Undesirable effects** Studies other than the included studies show that diaphragmatic breathing does not always have positive effects. These studies are excluded from the literature review in this guideline due to the study design, because often there were no comparisons with a control group. Two studies (Gosselink 1995; Vitacca 1998) indicate that diaphragmatic breathing has negative effects on, among other things, movements of the chest, mechanical efficiency and the degree of dyspnoea. According to (2002) and Gosselink (2004), the effect of diaphragmatic breathing is still unclear; it is still not yet clear from the literature for which patients diaphragmatic breathing is and is not effective. Diaphragmatic breathing cannot help severe COPD in the case of (severe) hyperinflation. With diaphragmatic breathing, the focus is on activating the diaphragm during respiration while at the same time minimising the activities of other muscle groups. In the event of severe COPD with hyperinflation, bad range of motion of the diaphragm due to hyperinflation is a reason for

the possible lack of effect and negative effects of diaphragmatic breathing on dyspnoea (Cahalin 2002). Diaphragmatic breathing is also deemed unsuitable for patients with Hoover's sign. The intervention should not be used in the presence of severe dyspnoea or severe hyperinflation.
The literature review in this guideline does show positive results with respect to dyspnoea and quality of life and functional capacity (with the last two outcome measures not being included in the other studies). This result is based on one study with 30 patients. The Yamaguti (2012) study also cites the above-mentioned studies and indicates that there are differences in the study design and population, among other things. Their intervention is showing positive results in this group of patients. Whether this is also the case in a group of patients with more severe COPD (like in the previously named studies) must be further investigated. Due to the limited evidence and target group in the Yamaguti study and the other additional considerations of the target group, the undesirable effects were set to moderate. The quality of the desirable effects is very low, according to GRADE.
**Balance between desirable and undesirable effects** Varying effects were seen in practice (just as in the literature). It is indicated that in the large majority of patients, the adverse effects are greater than the favou rable effects due to the presence of hyperinflation. Diaphragmatic breathing might have a positive effect on a small group of patients and could then be worthwhile.
**Value of desirable effects**Little value is attached to this; you cannot teach the diaphragmatic breathing tech nique to people with hyperinflation.
**Variation in value of desirable effects** The effects vary because effects depend in part on proper execution (depending on posture, relaxation and power) and the patient's context. There is still a lot of discussion about the effects in the literature.
**Required resources (costs)** Nothing additional is needed for applying this intervention. However, learning diaphragmatic breathing does take time, as does its application. This time is deducted from the treatment time that can also be dedicated to practicing. In addition, there are other breathing techniques (such as PLB), which take less time to learn and have the same effect. However, PLB has a different goal (PLB is aimed at dyspnoea) than diaphragmatic breathing (for facilitating ventilation) (Gosselink 2016). Learning diaphragmatic breathing can be an option for facilitating ventilation.
**Variation in required resources (costs)** None.
**Cost-effectiveness** No known studies.
**Acceptability** Due to content-related objections by experts from the field relating to modes of action and pos sible negative effects and the limited evidence, insufficient acceptability is likely.
**Feasibility** Given the limited acceptability, application of this intervention is not likely to be realistic.
There is one known RCT about diaphragmatic breathing that reported moderately positive results; however, the reported quality of evidence is low. The effects in practice and from the narrative literature vary greatly, and it is not yet clear for which patient group diaphragmatic breathing works or does not work. There are indications that applying diaphragmatic breathing in the presences of (severe) hyperinflation does not have added value, given that mobility of the diaphragm is not or is hardly possible anymore due to the hyperinflation.
It is also mentioned that diaphragmatic breathing should not be applied in the presence of Hoover's sign or severe dyspnoea. In general, a conditional recommendation is made against the use of diaphragmatic breath-ing. For patients with stable COPD (comparable to the patients in the study by Yamaguti 2012) that do not have hyperinflation (FEV1 about 42%), diaphragmatic breathing could be considered for promoting ventilation.

### Ventilation feedback

*Dyspnoea*
When comparing ventilation feedback versus no respiratory training, dyspnoea is measured with the Borg Scale or the MRC Dyspnoea Scale. Three studies (Borge 2015; Collins 2008; Van Gestel 2011) with 164 patients con-cluded that ventilation feedback has a *small effect* on dyspnoea in COPD patients compared to no respiratory training (SMD = -0.41; 95%-CI = -0.71 to -0.1).
The evidentiary value for the dyspnoea outcome measure was lowered by three levels given the limitations of the study design and execution (RoB) and the small number of patients (imprecision) for the Borge (2015), Collins (2008) and van Gestel (2011) studies. The evidentiary value is *very low*.

*Physical capacity*
The 6MWT is used to measure physical capacity when comparing ventilation feedback versus no respiratory training. Four weeks after the intervention, one study (Van Gestel 2011) in 40 patients concluded that ven-tilation has a *small effect* on physical capacity for COPD patients compared to no respiratory training (SMD = -0.33; 95%-CI = -0.95 to 0.30). Fifteen weeks after the intervention, one study (Collins 2008) in 33 patients concluded that ventilation technique has a small effect on physical capacity for COPD patients compared to no respiratory training (SMD = 0.44; 95%-CI = -0.25 to 1.13).

The evidentiary value for the physical capacity outcome measure when comparing ventilation feedback versus no respiratory training after four weeks was lowered by three levels given the limitations of the study design and execution ('risk of bias') and the small number of patients (imprecision) (Van Gestel 2011). De evidentiary value is *very low*.
The evidentiary value for the physical capacity outcome measure when comparing ventilation feedback versus no respiratory training after 15 weeks was lowered by three levels given the limitations of the study design and execution (RoB) and the small number of patients (imprecision), and the risk of publication bias appears to be real (Collins 2008). The evidentiary value is *very low*.

***Quality of life***
Quality of life is measured using the SGRQ when comparing ventilation feedback versus no respiratory training. Three studies (Borge 2015; Collins 2008; Van Gestel 2011) with 166 patients concluded that ventilation technique has a *small effect* on quality of life for COPD patients compared to no respiratory training (SMD = 0.20; 95%-CI = -0.32 to 0.72).
The evidentiary value for the quality of life outcome measure was lowered by three levels given the limitations of the study design and execution (RoB), the contradictory results (inconsistency) and the small number of patients (imprecision) for the Borge (2015), Collins (2008) and van Gestel (2011) studies. The evidentiary value is *very low*.

***Undesirable effects***
The risk of adverse effects is unknown; these have not been reported.
No GRADE assessment of the evidentiary value was performed for adverse effects; there are no studies that report adverse effects.

An overview of the effects and the evidentiary value for all outcomes is provided in the following table.

*GRADE evidence profile for ventilation feedback*

| **RCTs (*n*)** | **Quality assessment** | | | | | **Summary of results** | | | **GRADE** |
|---|---|---|---|---|---|---|---|---|---|
| | Study design and execution | Inconsistency | Indirectness | Imprecision | Publication bias | Patients (*n*) | | Effect size | |
| | | | | | | I | C | SMD (95%-CI) | |
| **Dyspnoea** | | | | | | | | | |
| 3 | 2 levels[a] | none | none | 1 level[b] | none | 83 | 81 | SMD = -0,41 (-0,71 tot -0,1) | very low |
| **Functional/physical capacity after 4 weeks** | | | | | | | | | |
| 1 | 2 levels[a] | none | none | 1 level[b] | none | 20 | 20 | SMD = -0,33 (-0,95 tot 0,30) | very low |
| **Functional/physical capacity after 15 weeks** | | | | | | | | | |
| 1 | 2 levels[a] | none | none | 1 level[b] | 1 level[c] | 17 | 16 | SMD = 0,44 (-0,25 tot 1,13) | very low |
| **Quality of life** | | | | | | | | | |
| 3 | 2 levels[a] | 1 level[d] | none | 1 level[b] | none | 84 | 82 | SMD = 0,20 (-0,32 tot 0,72) | very low |

I = intervention group; C = control group. SMD = standardized mean difference.
a Low risk of bias (RoB): randomisation adequate + allocation concealed + intention to treat (ITT); high RoB: < 3 items low risk; moderate RoB: other.
b Dichotomous outcome measure for population (*n* > 300); continuous measure of outcome for population (*n* > 400)
c The risk of publication bias appears to be real.
d I2 > 40%.

### Considerations for ventilation feedback

The considerations and recommendations stem from the deliberations held in the guideline panel based on the evidence-to-decision forms. See appendix C.4.2.

The considerations concerned:
**Adverse effects** There is a slight effect for all three outcome measures for ventilation feedback (at rest and during exercise).
**Undesirable effects** Ventilation feedback is not suitable for every patient because it takes a lot of energy.
**Quality of desirable effects** This is very low according to GRADE.
**Balance between desirable and undesirable effects** In general, there are no serious adverse effects but there are slight positive effects of this breathing technique. The favourable effects probably outweigh the adverse effects.
**Value of desirable effects** Value is attached to ventilation feedback. It is important for patients to learn to feel/experience/assess how they are doing, which facilitates empowerment. This way you give feedback to the patient about something he/she is already unconsciously doing and you can easily explain aspects and encourage the patient to experiment with them. It helps to give instructions and take measurements.
**Variation in value of desirable effects** There is a moderate variation in effects because ventilation feedback cannot be applied to every patient as this technique requires lots of energy on the patient's part. You can only use ventilation feedback at the practice itself; the patient cannot take the equipment home.
**Required resources (costs)** A very expensive device is needed that measures the degree of inspiration and expiration and provides feedback on this. This device also has specific software that the patient cannot take home.
**Variation in required resources (costs)** There are various devices available, but the variation in costs is not very high.
**Cost-effectiveness** No known studies.
**Acceptability** Ventilation feedback may not be acceptable given the limited effectiveness and high costs.
**Feasibility** Probably not acceptable.

Ventilation feedback has a slight effect, and the equipment is expensive to acquire. This intervention can be done by a therapist who has the equipment at his/her practice. It is better not to apply the intervention if the patient is too fatigued for this. This consideration resulted in a conditional recommendation against this therapy in general. Should the therapist have the equipment at his/her practice, then the equipment can be used to provide some insight.

### Combined respiratory interventions

*Dyspnoea*
Dyspnoea is measured when comparing combined breathing techniques versus no respiratory training. Three studies (Valenza 2014; Xi 2015; Zhang 2008) with 138 patients concluded that combined breathing techniques have a *large effect* on dyspnoea for COPD patients compared to no respiratory training (SMD = -0.90; 95%-CI = -1.90 to 0.11).
The evidentiary value for the dyspnoea outcome measure was lowered by two levels given the limitations of the study design and execution (RoB) and by one level given the small number of patients (imprecision) for the Valenza (2014), Xi (2015) and Zhang (2008) studies. The evidentiary value is *very low*.

*Physical capacity*
The 6MWT is used to measure physical capacity when comparing combined breathing techniques versus no respiratory training. Eight weeks after the intervention, one study (Zhang 2008) in 32 patients concluded that combined breathing techniques have a *very large effect* on physical capacity for COPD patients compared to no respiratory training (SMD = 4.53; 95%-CI = 3.15 to 5.90). Another study (Xi 2015) in 60 patients concluded that immediately after a one-year intervention combined breathing techniques have a *very large effect* on physical capacity for COPD patients compared to no respiratory training (SMD = 2.35; 95%-CI = 1.69 to 3.02).
The evidentiary value for the physical capacity outcome measure eight weeks after the intervention was lowered by two levels given the limitations of the study design and execution (RoB) and by one level given the small number of patients (imprecision) for the Zhang (2008) study. The evidentiary value is *very low*.
The evidentiary value for the physical capacity outcome measure after one year (immediately after the intervention) was lowered by two levels given the limitations of the study design and execution (RoB) and by one level given the small number of patients (imprecision) for the Xi (2015) study. The evidentiary value is *very low*.

***Quality of life***

Quality of life is measured using the SGRQ when comparing combined breathing techniques versus no respiratory training. Two studies (Xi 2015; Zhang 2008) with 92 patients concluded that combined breathing techniques have a *small effect* on quality of life for COPD patients compared to no respiratory training (SMD = -0.91; 95%-CI = -1.35 to -0.48).

One study (Sun 2003) in 89 patients concluded that, according to the CAI, combined breathing techniques have a *large effect* on quality of life for COPD patients compared to no respiratory training (SMD = -0.89 (95%-CI = -1.32 to -0.45).

The evidentiary value for the quality of life outcome measure was lowered by two levels given the limitations of the study design and execution (RoB) and by one level given the small number of patients (imprecision) for the Xi (2015) and Zhang (2008) studies. The evidentiary value is *very low*.

The evidentiary value for the quality of life outcome measure with the total score on the CAI was lowered by two levels given the limitations of the study design and execution (RoB) and by one level given the small number of patients (imprecision) for the Sun (2003) study. The evidentiary value is *very low*.

***Adverse effects***

The risk of adverse effects is unknown; these have not been reported.

No GRADE assessment of the evidentiary value was performed for adverse effects; there are no studies that report adverse effects.

An overview of the effects and the evidentiary value for all outcomes is provided in the following table.

***GRADE evidence profile for other/combined respiratory interventions***

| **RCTs (*n*)** | **Quality assessment** | | | | | **Summary of results** | | | **GRADE** |
|---|---|---|---|---|---|---|---|---|---|
| | Study design and execution | Inconsistency | Indirectness | Imprecision | Publication bias | Patients (*n*) | | Effect size | |
| | | | | | | I | C | SMD (95%-CI) | |
| **Dyspnoea** | | | | | | | | | |
| 3 | 2 levels[a] | none | none | 1 level[b] | none | 70 | 68 | SMD = -0,90 (-1,90 tot 0,11) | very low |
| **Functional/physical capacity after 8 weeks** | | | | | | | | | |
| 1 | 2 levels[a] | none | none | 1 level[b] | none | 17 | 15 | SMD = 4,53 (3,15 tot 5,90) | very low |
| **Functional/physical capacity after 1 year, immediately after intervention** | | | | | | | | | |
| 1 | 2 levels[a] | none | none | 1 level[b] | none | 30 | 30 | SMD = 2,35 (1,69 tot 3,02) | very low |
| **Quality of life** | | | | | | | | | |
| 2 | 2 levels[a] | none | none | 1 level[b] | none | 47 | 45 | SMD = -0,91 (-1,35 tot -0,48) | very low |
| **Quality of life CAI scale** | | | | | | | | | |
| 1 | 2 levels[a] | none | none | 1 level[b] | none | 45 | 44 | SMD = -0,89 (-1,32 tot -0,45) | very low |

CAI = central apnoea index; SMD = standardized mean difference.

a Low risk of bias (RoB): randomisation adequate + allocation concealed + intention to treat (ITT); high RoB: < 3 items low risk; moderate RoB: other.

b Dichotomous outcome measure for population (*n* > 300); continuous measure of outcome for population (*n* > 400)

### Considerations for combined respiratory interventions

The considerations and recommendations stem from the deliberations held in the guideline panel based on the evidence-to-decision forms. See appendix C.4.2.

The considerations concerned:
**Desirable effect** There is a (very) large effect for all three outcome measures.
**Undesirable effects** Good individual supervision is possible here, and there are no undesirable effects.
**Quality of desirable effects** Very low according to GRADE.
**Balance between desirable and undesirable effects** In general, there are no undesirable effects but there are primarily positive effects of a combined intervention. The favourable effects outweigh the adverse effects.
**Value of desirable effects** A combination of respiratory interventions offers the possibility of figuring out together with the patient what works in the patient's daily setting. Above all, keep it functional and try various options. PLB is applied in all studies, and this may explain the large effect. It is important to apply PLB in any case.
**Variation in value of desirable effects** There is some variation in the effects because sometimes it takes a while to determine what works for a patient and because coordination of various interventions requires some effort. Focus on one technique and don't try to do too much at the same time. Effects can counteract each other or be incompatible, e.g. like PLB cannot be applied in combination with diaphragmatic breathing. Start with one technique and then see where supplementation is needed; the choice depends on the goal.
**Required resources (costs)** It depends on which interventions you combine.
**Variation in required resources (costs)** It depends on the combination of interventions; the variation may be moderate due to this.
**Acceptability** A combination of breathing techniques appears to be acceptable.
**Feasibility** A combination of breathing techniques appears to be feasible.

A combined respiratory intervention is experienced as a very pleasant intervention because such an intervention enables individual supervision and customised care. It is a safe and easy to apply intervention with positive results and has no undesirable effects. There is some variation in the effects because sometimes it takes a while to determine what works for a patient, and coordination of various interventions requires some effort. PLB appears to be important in any case.
This has resulted in a conditional recommendation for combined respiratory intervention, with at least PLBbeing applied. In addition, the application of respiratory interventions should be combined with exercise interventions. The techniques should be learned for those activities of daily life that are difficult for the patient due to dyspnoea. The recommendation is to not immediately teach multiple breathing techniques but to first teach one breathing technique and then assess which additional respiratory intervention could be of added value.

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## Note C.4.3 Relaxation techniques

### Clinical question

**Which relaxation techniques can be performed to decrease dyspnoea?**

### Literature

To answer the clinical question*, it was decided in consultation with the guideline panel and the review panel not to conduct a systematic review. The literature about this topic was collected in a non-systematic manner and is mentioned in the literature list below.

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* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

### Note C.4.4 Posture adjustments

#### Clinical question

**What is the best posture for decreasing dyspnoea?**

To answer the clinical question*, it was decided in consultation with the guideline panel and the review panel not to conduct a systematic review. The literature about this topic was collected in a non-systematic manner and is mentioned in the literature list below..

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### Note C.4.5 Mucus clearance

#### Clinical question

**Which techniques for facilitating mucus clearance are indicated for COPD?**

This clinical question is further divided into the following sub-questions:

1. Which techniques for facilitating mucus clearance are indicated for patients with stable COPD?
2. Which techniques for facilitating mucus clearance are indicated for COPD patients with an exacerbation?

#### Literature

To answer these clinical questions*, a systematic review was performed.
Various techniques are considered together under breathing techniques, such as the active cycle of breathing technique (ACBT), the forced expiration technique (FET), autogenic drainage (AD) and/or expiration with an open glottis in the lateral posture (ELTGOL).
Interventions that are applied to a very limited extent, such as intrapulmonary percussive ventilation (IPV or IPPV) and high-frequency chest wall oscillation (HFCWO), just as conventional interventions that are hardly applied anymore, such as percussion and vibration, were not taken into consideration. Draining of the airways, breathing techniques for purposes other than mucus clearance such as pursed-lip breathing (see C4.2 'Breathing techniques'), interventions for hyperinflation during exercise and training of the respiratory muscles (see C4.1 'Respiratory muscle training') were also not considered.

**Outcome measures**

With stable COPD, quality of life, dyspnoea, exacerbations, lung-related hospitalisation and physical capacity (desirable effects) and minor adverse events and mortality (undesirable effects) are listed as patient-relevant outcome measures crucial and important to the decision-making process.
For an exacerbation, these are the following outcome measures: quality of life, dyspnoea, length of hospital/IC stay (length of stay [LOS]), ventilation (invasive/non-invasive, duration), physical capacity and future exacerbations and lung-related hospitalisations (desirable effects) and minor adverse events and mortality (undesirable effects).

* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

Although outcome measures such as FEV and degrees of mucus clearance have been reported in many studies, these are not good indicators of success for the effectiveness of interventions for facilitating mucus clearance The degrees of lung function do not correlate well with patient-relevant outcome measures, and degrees of mucus clearance are difficult to interpret (Osadnik 2014).
In some studies (e.g. Mascardi 2016; Nicolini 2014, 2018a), dyspnoea was measured with multiple instruments. Only the results of one measurement instrument can be processed per outcome measure in order to prevent over-representation in these studies. When both the modified Medical Research Council Dyspnoea questionnaire (mMRC) and the BCSS were used in the same study population, it was decided to include the results of the mMRC in the meta-analysis because the mMRC enjoys wider renown than the BCSS and is therefore easier to interpret.

**Search and selection**

*Search*
The starting point for this review was the systematic review (SR) by Osadnik (2012) on the effectiveness of different interventions for facilitating mucus clearance in patients with stable COPD and patients with a COPD exacerbation. A systematic search with relevant search terms on 3 August 2018 searched for new (as of 1 January 2012) randomised controlled studies (RCTs) in the databases PubMed, EMBASE, CENTRAL, Cochrane Library, PeDRO and EmCare for supplementing and updating this review. This yielded 549 hits.

*Literature selection*
The literature was selected and then analysed for:
- mucus clearance in the presence of stable COPD;
- mucus clearance in the presence of an exacerbation.

### 1 Mucus clearance in the presence of stable COPD

A total of 14 studies were selected for the review on mucus clearance in the presence of stable COPD ($n$ = 14). This is eight studies from the Osadnik review (2012: Cegla 1997, 2002; Christensen 1990, 1991a,b; Weiner 1996; Wolkove 2002, 2004). Then six recent articles were added to this based on a systematic review (Fridlender 2012; Gastaldi 2015; Mascardi 2016; Nicolini 2014, 2018a; Sethi 2014). Then randomised controlled trials (RCTs) from other reviews (such as Andrews 2013; Fagevik 2009; Ides 2011; Lewis 2012; McCool 2006; Reychler 2018; Strickland 2013) were assessed based on the selection criteria. This ultimately did not yield any new trials. The total number of studies in this review for mucus clearance in the presence of stable COPD therefore amounts to 14.

The selection criteria for studies on interventions in the presence of stable COPD are included in the following table.

| *Selection criteria* | |
|---|---|
| Type of studies | RCTs (parallel and cross-over) |
| Type of patients | patients with stable COPD (COPD in > 50% of the study population) |
| Type of interventions | treatment for facilitating mucus clearance: breathing techniques (ACBT, autogenic drainage, forced expiration, FET, ELTGOL), PEP devices and PEP devices with oscillation |
| Type of comparisons | placebo therapy or usual care* |
| Type of outcomes (desirable and undesirable effects) | • quality of life, dyspnoea, exacerbations and lung-related hospitalisations and physical capacity (desirable effects) and adverse events and mortality (undesirable effects) 'crucial outcome measures': physical exercise capacity, quality of life, dyspnoea, exacerbations, physical functioning in ADL<br>• 'important outcome measures': peripheral muscle strength and adverse events |

| | |
|---|---|
| Type of timeline | immediately after the intervention |
| Other | published in English or Dutch |

ACBT = active cycle of breathing technique; FET = forced expiration technique; ELTGOL = expiration with an open glottis in the lateral posture; PEP = positive expiratory pressure.
* Studies that directly compare two interventions with each other without a control group were not included in this review, but studies that investigated two interventions and had a control group are included. This concerns the Nicolini (2018b) study on HFCWO and PEP, Nicolini (2018a) study on PEP and O-PEP and Nicolini (2014) study on IPPB and PEP. These studies with three groups (control group, intervention group 1 and intervention group 2) appear in this review in two comparisons (intervention 1 versus control group and intervention group 2 versus control group).

The lack of clinically relevant outcome measures was the most frequent reason for exclusion. More information about the reasons for exclusion are listed in appendix C.4.5.

**Literature summary**

***Description of studies***
The review consists of 15 studies with a total of 645 patients with stable COPD. The average age of the patient populations varied between 54 (Christensen 1991a) and 72 (Nicolini 2014, 2018a) years. The lung function (air-flow limitation expressed in FEV) of patients varied between 0.75 l (Wolkove 2002) and 2.1 l (Christensen 1991b) or between 29% (Wolkove 2002) and 50% (Sethi 2014) of the predicted value. Experienced symptom burden such as this is measured with the COPD Assessment Test (CAT) varying between 23 (Mascardi 2016) and 27 (Nicolini 2014).

The included studies evaluate the effectiveness of two different interventions, specifically positive expiratory pressure (PEP) and PEP with oscillation (O-PEP).

***Overview of interventions for facilitating mucus clearance with associated studies***

| Intervention | Abbreviation | Explanation | Studies |
|---|---|---|---|
| positive expiratory pressure | PEP | temporary (T-PEP) or intermittent (I-PEP) expiration for a fixed resistance due to which the pressure in the airways is increased | Christensen 1990, 1991a,b,<br>Mascardi 2016<br>Nicolini 2014, 2018a |
| oscillating positive expiratory pressure | O-PEP | expiration against vibrating air resistance, also known under brand names such as Flutter, Cornet or Acapella | Cegla 1991, 2002<br>Weiner 1996<br>Wolkove 2002, 2004<br>Gastaldi 2015<br>Sethi 2014<br>Nicolini 2018a<br>Fridlender 2012 |
| breathing techniques | forced expiration, FET, AD, ACBT or ELTGOL | active breathing techniques for facilitating mucus clearance, specifically autogenic drainage (AD), active cycle of breathing technique (ACBT), forced expiration technique (FET), expiration with an open glottis in the lateral posture (ELTGOL) | no studies found that meet the inclusion criteria |

The control group received placebo therapy (e.g. the same device and mask without air pressure, or flutter without steel ball or only usual care

A detailed overview of the included studies is available online as 'Appendix Evidence Tables'

***Individual study quality (RoB)***

The study design and execution of all studies ('risk of bias', RoB) were assessed using the Cochrane RoB tool with low, high or unclear risk for six potential causes of bias, specifically random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues.
This assessment showed that the information about the method for determining the randomisation order and how this allocation was kept hidden is lacking in a large number of studies. In a number of studies, patients, personnel and outcome assessors were not blinded and there were also cross-over trials.
An overview of the individual study quality assessment (RoB) is provided in the following table.

***Risk of bias: Mucus clearance in the presence of stable COPD***

| | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|---|---|---|---|---|---|---|---|
| Cegla 1997 | ? | ? | − | − | + | − | ? |
| Cegla 2002 | ? | ? | − | − | + | − | − |
| Christensen 1990 | ? | ? | ? | + | − | − | + |
| Christensen 1991 | ? | ? | ? | − | − | + | + |
| Christensen 1991a | ? | ? | − | − | + | + | − |
| Fridlender 2012 | ? | ? | + | ? | − | ? | − |
| Gastaldi 2015 | + | ? | ? | ? | + | − | − |
| Mascardi 2016 | + | + | + | + | − | ? | ? |
| Nicolini 2014 | + | + | + | + | + | ? | ? |
| Nicolini 2018b | + | + | ? | ? | − | + | + |
| Sethi 2014 | + | + | − | − | + | + | + |
| Weiner 1996 | + | ? | ? | + | + | − | ? |
| Wolkove 2002 | ? | ? | − | − | ? | + | − |
| Wolkove 2004 | ? | + | − | − | ? | + | − |

+ = yes; − = no; ? = unclear

**Results and evidentiary value**

The results and evidentiary value of the following are described below:

- positive expiratory pressure (PEP) in patients with stable COPD;

- oscillating positive expiratory pressure (oscillating PEP, O-PEP) in patients with stable COPD;
- breathing techniques (autogenic drainage/ACBT/FET/ELTGOL) in patients with stable COPD.

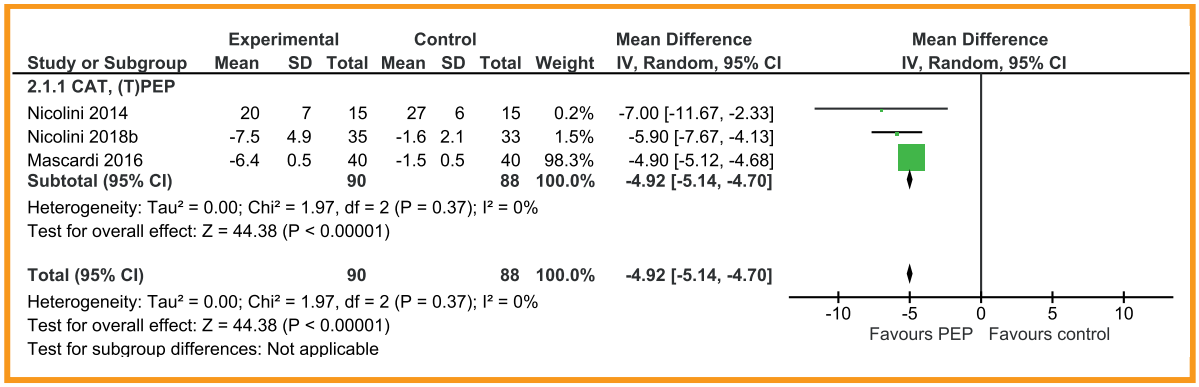
- ***Positive expiratory pressure (PEP) in patients with stable COPD***

*Quality of life*

Use of PEP brings about an enormous improvement in quality of life (Nicolini 2014, 2018a; Mascardi 2014). The intervention groups scored on average between 4.9 and 7.0 points lower on the CAT than the control group (MD = -4.92; 95%-CI = -5.14 to -4.70; *n* = 178). See the forest plot.

The evidentiary value for the quality of life was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision). The evidentiary value is therefore *low*.

*Forest plot of the mucus clearance for stable COPD: quality of life*




*Dyspnoea*

The effect of PEP on dyspnoea is enormous; the average difference on the mMRC in the studies of Mascardi (2016) and Nicolini (2014, 2018a) was -0.65 points (95%-CI = -0.85 to -0.45; *n* = 178) in favour of PEP. However, two earlier studies (Christensen 1990, 1991b; *n* = 85) found no effect of PEP on dyspnoea with other measurement instruments.

The evidentiary value for dyspnoea was lowered by three levels given the limitations of the study design and execution and the small number of patients (imprecision). The evidentiary value is therefore *low*.

*Physical capacity and/or physical functioning*

PEP brings about an enormous improvement of physical capacity when measuring this with the 6MWT (Mascardi 2016; Nicolini 2018a). The average increase in walking distance was 30.8 metres (95%-CI = 16.9 to 44.8; *n* = 133). However, Christensen 1990 (*n* = 47) shows a non-significant worsening in self-reported physical functioning. Patients reported the maximum level of physical activity that was limited by dyspnoea on a 20 cm VAS (negative values represent improvement). The median score (range) in the PEP group was 4 mm (-88 to 115) and in the control group -1 mm (-88 to 83; not significant).

The evidentiary value for physical capacity was lowered by two levels given the limitations of the study design and the small number of patients (imprecision). The evidentiary value is therefore *low*.

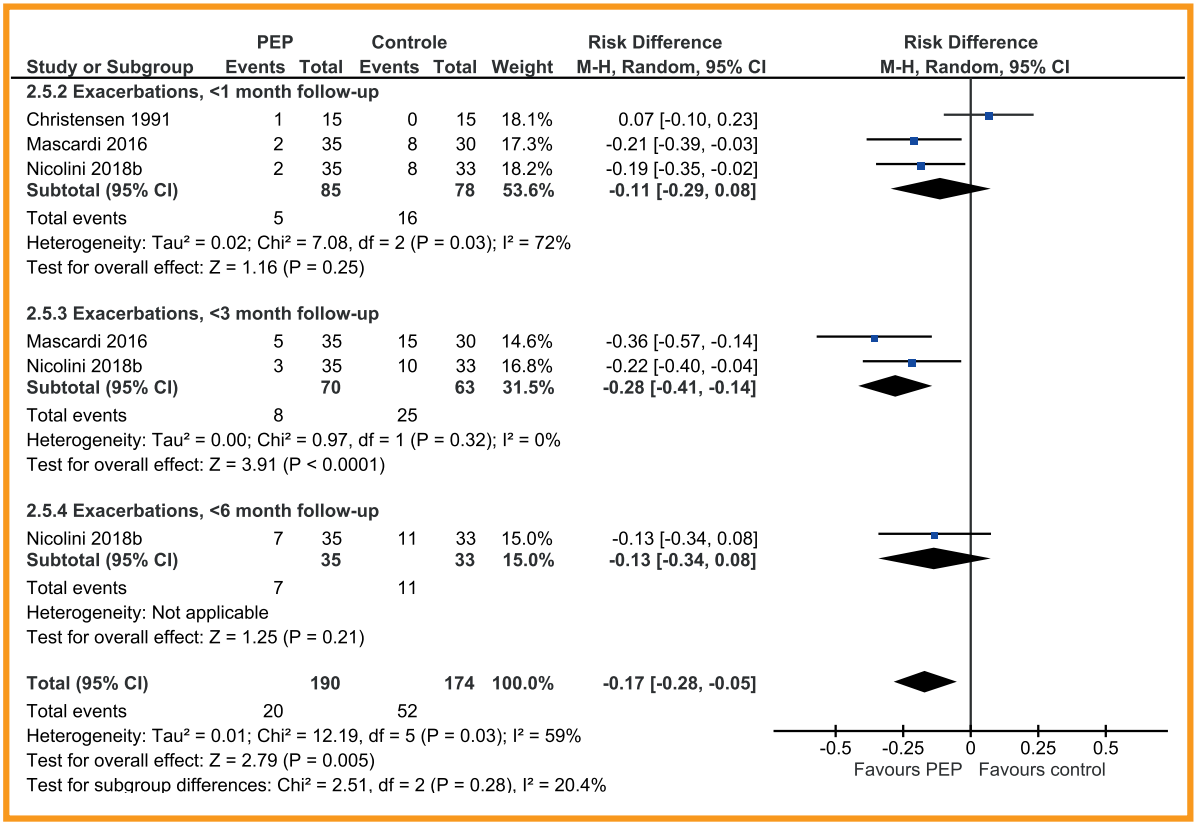
*Exacerbations*

Four studies reported the effect of PEP on the risk of an exacerbation (Christensen 1990, 1991b; Mascardi 2016; Nicolini 2018a).

Christensen 1990 (*n* = 60) did not find any significant differences in the number of exacerbations (no data reported). In the other studies, the risk of an exacerbation within one month after PEP was lowered by 11% (95%-CI = -0.29 to 0.08; *n* = 163) (Christensen 1991b, Mascardi 2016, Nicolini 2018a). In the three months after PEP, the risk of exacerbations was lowered by 28% (95%-CI = 0.41 to -0.14; *n* = 133) (Mascardi 2016, Nicolini 2018a). And in the six months after PEP the risk was decreased by 13% (95%-CI = -0.34 to 0.08; *n* = 68; Nicolini 2018a). See the forest plot.

The evidentiary value for the risk of exacerbations was lowered by three levels given the limitations of the study design and execution and the small number of patients (imprecision). The evidentiary value is therefore *low*.

*Forest plot of mucus clearance for stable COPD: risk of exacerbations*




***Lung-related hospitalisation***

The effect of PEP on lung-related hospitalisations is reported in Christensen 1990 (*n* = 60). This study did not find any significant differences in the number of hospitalisations or length of hospital stay (no data reported). The evidentiary value for lung-related hospitalisation was lowered by three levels given the limitations of the study design and execution and by two levels due to the small number of patients (imprecision). The evidentiary value is therefore *very low*.

***Undesirable effects***

The studies by Christensen (1990, 1991a,b) report that no undesirable effects of PEP occurred during the study period (*n* = 87).

The evidentiary value for the lung-related hospitalisation was lowered by three levels given the limitations of the study design and execution and the very small number of events and patients (imprecision). The evidentiary value is therefore *very low*.

An overview of the effects and the evidentiary value for all outcome measures is provided in the following table.

*GRADE evidence profile: PEP for facilitating mucus clearance in patients with stable COPD*

| RCTs (*n*) | Quality assessment | | | | | Summary of results | | | GRADE |
|---|---|---|---|---|---|---|---|---|---|
| | Study design and execution | Inconsistentie | Inconsistency | Imprecision | Publication bias | Patients (*n*) | | Effect size | |
| | | | | | | I | C | MD/SMD/RD (95%-CI) | |
| **Quality of life** | | | | | | | | | |
| 3 | 1 level | none | none | 1 level | none | 90 | 88 | enormous improvement of CAT: MD = -4.92 (-5.14 to-4.70) | low |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Dyspnoea** | | | | | | | | | |
| 5 | 1 level | none | none | 1 level | none | 90 | 88 | enormous improvement on the mMRC: MD = -0.65 points (-0.85 to -0.45) | low |
| | | | | | | 75 | | no effect on other measures | |
| **Physical capacity and/or physical functioning** | | | | | | | | | |
| 3 | 1 level | none | none | 1 level | none | 95 | 85 | enormous improvement on the 6MWT: MD = 30.8 (16.9 to 44.8) m (*n* = 133)<br>self-reporting: no effect (*n* = 47) | low |
| **Exacerbations** | | | | | | | | | |
| 3 | 1 level | none | none | 1 level | none | 115 | 108 | risk of exacerbation (RD):<br>-11% (-29 to 8) after 1 month,<br>-28% (-41 to -14) after 3 months,<br>-13% (-34 to 08) after 6 months<br>no risk difference (no data; *n* = 60) | very low |
| **Lung-related hospitalisation** | | | | | | | | | |
| 1 | 1 level | none | none | 2 levels | none | 60 | NS | very low | very low |
| **Adverse events** | | | | | | | | | |
| 3 | 1 level | none | none | 2 levels | none | 87 | RD = 0 | very low | very low |

I = intervention group; C = control group. CAT = COPD Assessment Test; RD = risk difference; MD = median difference; mMCR = modified Medical Research Council Dyspnoea questionnaire; 6MWT = Six Minute Walk Test.

- ***Oscillating positive expiratory pressure (oscillating PEP, O-PEP) in patients with stable COPD***

*Quality of life*

Oscillating positive expiratory pressure (O-PEP) may result in a large improvement of quality of life (Nicolini 2018a; Weiner 1996; Wolkove 2004), although not all studies confirm this (Fridlender 2012). Patients with O-PEP score a lot better on the CAT (MD = 4.8 points lower, 95%-CI = -5.9 to -3.7; *n* = 69; Nicolini 2018a), and a clinically relevant improvement (MCID = 4 points; Jones 1991) occurs on the St George's Respiratory Questionnaire (SGRQ: MD = 6.1 points lower, 95%-CI = -8.9 to -3.3; *n* = 15; Wolkove 2004). Even the self-reported general well-being improved significantly (no data reported, Weiner 1996; *n* = 20). However, one study does not show a significant difference on the Chronic Respiratory Disease Questionnaire (CRQ; no data reported, Fridlender 2012, *n* = 22).

The evidentiary value for the quality of life was lowered by two levels given the limitations of the study design and execution (such as no blinding) and the small number of patients (imprecision). The evidentiary value is therefore low.

*Dyspnoea*

Treatment with O-PEP decreases the degree of dyspnoea (Nicolini 2018a; Sethi 2014; Weiner 1996; Wolkove 2002, 2004). Patients with O-PEP treatment score an average of 0.5 (95%-CI = -0.8 to -0.2; *n* = 138) points lower on the mMRC (Nicolini 2018a, Sethi 2014), exhibit a significant long-term improvement of dyspnoea (no data reported; *n* = 20; Weiner 1996) and after O-PEP exhibit a significant but not clinically relevant (MCID Borg Scale = 1.0 point; Borg 1982; Solway 2002) decrease of -0.3 points on the Borg Scale for dyspnoea (95%-CI = -0.5 to -0.1; *n* = 23; Wolkove 2002). Finally, after one week of O-PEP treatment during the 6MWT, patients had 0.5 point less increase of dyspnoea on the Borg Scale, despite a longer walking distance ($p < 0.05$; *n* = 15; Wolkove 2004). However, one study did not show a significant difference on the CRQ Dyspnoea Sub-scale (no

data reported, Fridlender 2012, *n* = 22). The evidentiary value for dyspnoea was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision). The evidentiary value is therefore low.

***Physical capacity and/or physical functioning***

0-PEP results in large improvements in physical capacity when measured with the 6MWT (Nicolini 2018a; Sethi 2014, Wolkove 2002, 2004) and 12MWT (Weiner 1996).

In the Nicolini 2018a and Stehi 2014 studies, patients walked an average of 25.6 metres farther in six minutes after 0-PEP treatment (95%-CI = 5.6 to 45.6; *n* = 138). In the Weiner (1996) study, patients walked an average of 111.0 metres farther than the control group in 12 minutes after 0-PEP treatment (95%-CI = 66.5 to 155.5; *n* = 20).

The Wolkove (2002, 2004) studies also show significant improvements on the 6MWT with an average 12.9 metre increase in walking distance (95%-CI = 6.0 to 19.9; *n* = 38), just like the Fridlender study (no data reported; *n* = 22).

The evidentiary value for the quality of life was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision). The evidentiary value is therefore low.

***Exacerbations and lung-related hospitalisation***

During and within one month after 0-PEP, the risk of exacerbations and lung-related hospitalisations decreased significantly by 16% (95%-CI = -30% to -3%; *n* = 138; Sethi 2014; Nicolini 2018a). In these studies, the number of exacerbations during the six-month intervention period was 21% lower (95%-CI = -0.41 to -0.00; Sethi 2014; *n* = 69) and in the month after the end of the 12-day 0-PEP treatment the number of exacerbations was 13% lower (95%-CI = -0.31 to 0.05; Nicolini 2018a).

In the long term, Cegla 2002 (*n* = 50) found a significant decrease in the number of lung-related hospitalisations of 28% (95%-CI -0.53 to -0.03). Nicolini 2018a (*n* = 69) found a decrease of 8% three months after 0-PEP (95%-CI =-29% to 13%) and a decrease of 8% six months after 0-PEP (95%-CI = -30% to 13%).

The evidentiary value for exacerbations and lung-related hospitalisations was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision). The evidentiary value is therefore low.

***Undesirable effects***

Undesirable effects of 0-PEP are not known; they have not been reported.

An overview of the effects and the evidentiary value for all outcome measures is provided in the following table.

***GRADE evidence profile: 0-PEP for facilitating mucus clearance in patients with stable COPD***

| **RCTs (*n*)** | **Quality assessment** | | | | | **Summary of results** | | | **GRADE** |
|---|---|---|---|---|---|---|---|---|---|
| | Study design and execution | Inconsistency | Indirectness | Imprecision | Publication bias | Patients (*n*) | | Effect size | |
| | | | | | | I | C | MD/SMD/RD (95%-CI) | |
| **Quality of life** | | | | | | | | | |
| 4 | 1 level | none | none | 1 level | none | 126 | 88 | CAT: improvement (*n* = 69)<br>SGRQ: improvement (*n* = 15)<br>General well-being: improvement (*n* = 20)<br>CRQ: no improvement (*n* = 22) | low |
| **Dyspnoea** | | | | | | | | | |
| 6 | 1 level | none | none | 1 level | none | 218 | 88 | mMRC: large decrease (*n* = 138) Borg Scale:<br>small decrease (*n* = 23)<br>Unknown measurement instrument: significant effect<br>(*n* = 20); CRQ dyspnoea: no improvement (*n* = 22)<br>Also significantly less worsening of dyspnoea during the<br>6MWT despite the longer walking distance (*n* = 15) | low |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Physical capacity and/or physical functioning** | | | | | | | | | |
| 6 | 1 level | none | none | 1 level | none | 218 | 85 | 6 MWT en 12 MWT: longer walking distance | low |
| **Exacerbations and lung-related hospitalisation** | | | | | | | | | |
| 3 | 1 level | none | none | 1 level | none | 94 | 94 | Exacerbations:<br>- short term (≤ 1 month): RD = −0.16 (−0.30 to −0.03), *n* = 138)<br>- long term (6 months): RD = −8% (−30 to 13), (*n* = 69)<br>lung-related hospitalisation: RD = −28% (−0.53 to −0.03; *n* = 50 | low |
| **Adverse events** | | | | | | | | | |
| 0 | – | – | – | – | – | – | – | – | – |

I = intervention group; C = control group. CAT = COPD Assessment Test; CRQ = Chronic Respiratory Disease Questionnaire; RV = risk difference; MD = mean difference; mo = month(s); mMCR = modified Medical Research Council Dyspnoea questionnaire; 6MWT = Six Minute Walk Test; SGRQ = St George's Respiratory Questionnaire.

- ***Breathing techniques (autogenic drainage/ACBT/FET/ELTGOL) in patients with stable COPD***

No RCTs were found on the effects of breathing techniques (for facilitating mucus clearance) on quality of life, dyspnoea, physical capacity and/or physical functioning, exacerbations and lung-related hospitalisation, length of hospital stay or undesirable effects/events.

### 2 Mucus clearance in the presence of a COPD exacerbation

The selection criteria for studies on interventions in the presence of an exacerbation are included in the following table.

| *Selection criteria* | |
|---|---|
| Type of studies | RCTs (parallel and cross-over) |
| Type of patients | patients with an exacerbation (COPD in > 50% of the study population) |
| Type of interventions | treatment met breathing techniques, PEP devices, PEP devices with oscillation or manual techniques for facilitating mucus clearance |
| Type of comparisons | placebo therapy or usual care |
| Type of outcomes (desirable and undesirable effects) | quality of life, dyspnoea, length of stay (hospital/IC), physical capacity and future exacerbations and lung-related hospitalisations (desirable effects) and adverse events and mortality (undesirable effects). |
| Type of timeline | immediately after the intervention |
| Other | published in English or Dutch |

Just as with the literature on mucus clearance in the presence of stable COPD, the lack of clinically relevant outcome measures was the most frequent reason for exclusion. More information about the reasons for exclusion are listed in the appendix.

A total of 6 studies were selected for the review on mucus clearance in the presence of an exacerbation (*n* = 6). The review on mucus clearance in the presence of an exacerbation includes three studies from the Osadnik (2012) review (Bellone 2002; Kodric 2009; Inal-Ince 2004). Another three articles were added to the review (Osadnik 2014; Basri 2017; Cross 2012) as a result of the search. Trials from other reviews (such as Tang 2010; Hill 2010; Andrews 2013; Fagevik 2009; Reychler 2018; Ides 2011; Strickland 2013; Lewis 2012) were also assessed based on the selection criteria. This ultimately did not yield any new trials. The total number of studies in this review on the effects of mucus clearance in the presence of an exacerbation therefore amounts to six (Basri 2017; Bellone 2002; Cross 2012; Inal-Ince 2004; Kodric 2009; Osadnik 2014).

**Literature summary**

*Description of studies*

The review consists of six articles with a total of 802 patients with a COPD exacerbation who were hosptalised. The average age of the patient population is between 54 and 70 years. The included studies evaluate the effectiveness of three different interventions: 1) breathing techniques (such as active cycle of breathing tech nique, autogenic drainage or forced expiration techniques), 2) manual techniques (postural drainage, per cussion, vibration) and 3) positive expiratory pressure (PEP). The control group received placebo therapy (e.g. the same device and mask without air pressure) or only the usual care. A brief description of the interventions is provided in the following table.

*Overview of interventions for facilitating mucus clearance in the presence of stable COPD, with associated studies*

| Intervention | Abbreviation | Definition | Studies |
|---|---|---|---|
| breathing techniques | ACBT / AD / BD / ELTGOL / FET | breathing techniques such as active cycle of breathing technique (ACBT), autogenic drainage (AD) and bronchial drainage (BD) such as expiration with the glottis open (ELTGOL) and forced expiration technique (FET) | Basri 2017 (ACBT) Kodric 2009 (ELTGOL) Inal-Ince 2004 (ACBT) |
| positive expiratory pressure | PEP | temporary (T-PEP) or intermittent (I-PEP) expiration for a fixed resistance due to which the pressure in the airways is increased | Bellone 2002 Osadnik 2014 |
| oscillating positive expiratory pressure | O-PEP | expiration against vibrating air resistance (e.g. Flutter©, Cornet© or Acapella©) | no studies were found |
| manual/conventional/ passive chest physiotherapy | CPT | manual/conventional/passive chest physiotherapy and vibration | Cross 2012 |

A detailed overview of the included studies is available online as 'Appendix Evidence Tables'.

*Individual study quality*

The study design and execution of all six studies ('risk of bias', RoB) were assessed using the Cochrane RoB tool with low, high or unclear risk for six potential causes of bias, specifically random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues.
This assessment showed that the information about the method for determining the randomisation order and how this allocation was kept hidden is lacking in a large number of studies. In a number of studies, patients, personnel and outcome assessors were not blinded and there were also cross-over trials.
An overview of the study quality assessment (RoB) per study is provided in the following table.

*Risk of bias: Mucus clearance in the presence of a COPD exacerbation*


\+ = yes; – = no; ? = unclear

**Results and evidentiary value**

The results and evidentiary value of the following are described below:

- breathing techniques in patients with a COPD exacerbation;
- manual techniques in patients with a COPD exacerbation;
- Positive expiratory pressure (PEP) in patients with a COPD exacerbation;
- PEP with oscillation (oscillating-PEP, O-PEP) in patients with a COPD exacerbation.

- ***Breathing techniques in patients with a COPD exacerbation***

*Quality of life*

Treatment with ELTGOL did not show a difference in quality of life when measured with the SGRQ (MD = 0.30; 95%-CI = -9.13 to 9.73; *n* = 59; Kodric 2009).

The evidentiary value for the quality of life was lowered by three levels given the limitations of the study design and execution and the very small number of patients (imprecision) and is therefore *very low*.

*Dyspnoea*

ELTGOL decreases dyspnoea during exercise, measured here with the Borg Scale (MD = -1.30; 95%-CI = -2.14 to -0.46; *n* = 59; Kordic 2009). ABCT also showed an enormous improvement of dyspnoea (MD = -4.38; 95%-CI = -4.84 to -3.92; *n* = 60) in the Basri (2017) study, which was measured with the 100 mm VAS in this study. However, no difference in difference in dyspnoea in ADL is measured on the ELTGOL, done with the MRC in this study (MD = -0.40; 95%-CI = -1.04 to 0.24; *n* = 59; Kordic 2009).

The evidentiary value for dyspnoea was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision) and is therefore *low*.

***Physical capacity and/or physical functioning***
No studies were found on the effect of breathing techniques for facilitating mucus clearance on physical capacity or physical functioning.

***Ventilation***
The risk of ventilation was -6% lower after ACBT (95%-CI = -24% to 11%; *n* = 27; Inal-Ince 2004).
With regard to the duration of the ventilation, the number of days with NIV after ACBT was 1.7 days shorter (MD = -1.70 days; 95%-CI = -3.41 to 0.01) and NIV lasted 19 hours less with ACBT (MD = -19.20; 95%-CI = -41.61 to 3.21) compared to the control condition (Inal-Ince 2004; *n* = 34).
Invasive ventilation via endotracheal intubation was necessary in one patient in each group, with a risk difference of 0% (95%-CI = -16 to 16; *n* = 34; Inal-Ince 2004).
The evidentiary value for risk of ventilation and its duration was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision) and is therefore *low*.

***Length of hospital stay***
The hospitalisation duration was shortened by a half a day after use of ELTGOL (MD = -0.50; 95%-CI = -1.94 to 0.94; *n* = 59; Kodric 2009). Admission to the IC was shortened by 1.4 days after ACBT (length of hospital stay ACBT= 8.0 days, check-up = 9.4 days; MD = -1.40; 95%-CI = -4.19 to 1.39; *n* = 34; Inal-Ince 2004).
The evidentiary value for length of hospital stay was lowered by two levels given the limitations of the study design and execution and the very small number of patients (imprecision) and is therefore *very low*.

***Future exacerbations and lung-related hospitalisation***
Kodric (2009; *n* = 22) found a small decrease of the risk of future exacerbations and a very small decrease in lung-related hospitalisations (exacerbation: MD = -0.60; 95%-CI = -2.64 to 1.44; hospitalisation: MD = 0.40; 95%-CI = -1.35 to 2.15) six months after the use of ELTGOL during an exacerbation.
The evidentiary value for future exacerbations and lung-related hospitalisations was lowered by three levels given the limitations of the study design and execution and the very small number of patients (imprecision) and is therefore *very low*.

***Undesirable effects***
Adverse events consisted of pressure sores on the nose (ACBT= 7 patients; C= 6 patients), irritation of the eyes (ACBT= 2 patients; C= 1 patient), and one nosebleed in the control group (Inal-Ince 2004).
The evidentiary value for adverse events was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision) and is therefore *low*.

***Mortality***
In the Inal-Ince 2004 study, no deaths occurred in the short term in either group (RD = 0%; 95%-CI = -11 to 11; *n* = 34). There was also no difference in the long term (Kodric 2009); there was one death in both groups (RD = 0%; 95%-CI = -22 to 22; *n* = 24).
The evidentiary value for mortality was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision) and is therefore *very low*.

- ***Manual techniques for patients with a COPD exacerbation***

***Quality of life***
The large Cross study (2012; *n* = 372) showed a negligible null effect (SMD = -0.02) of the use of ACBT with manual pulmonary physiotherapy techniques consisting of postural drainage, percussion, vibration and coughing techniques compared to ACBT alone on quality of life, measured here with the SGRQ in patients who were hospitalised due to an exacerbation (MD = -0.36; 95%-CI = -4.31 to 3.59). An analysis of the various SGRQ subscales yielded the same image. The same study showed no effect for the quality of life using another measurement instrument either (EQ-5D score MD = -0.03; 95%-CI = -0.10 to 0.04; EQ-5D VAS MD = 0.96; 95%-CI = -3.37 to 5.29).
The evidentiary value for the quality of life was lowered by one level given the limitations of the study design and execution (such as blinding and drop-out). The evidentiary value is therefore *moderate*.

***Dyspnoea***
Manual pulmonary physiotherapy in patients with an exacerbation has no effect on symptoms of dyspnoea, cough and sputum, measured in this study with the BCSS (MD = -0.06; 95%-CI = -0.55 to 0.66; *n* = 372; Cross 2012).

The evidentiary value for dyspnoea was lowered by one level given the limitations of the study design and execution (such as blinding and drop-out). The evidentiary value is therefore *moderate*.

***Ventilation***
No studies were found on the effect of manual techniques in the presence of an exacerbation on the risk of or the duration of the ventilation.

***Length of hospital stay***
Use of manual pulmonary physiotherapy techniques has no effect on the number of hospitalisation days for six months of follow-up (RR= 1.07; 95%-CI = 0.91 to 1.24; *n* = 372; Cross 2012).
The evidentiary value for length of hospital stay was lowered by one level given the limitations of the study design and execution (such as blinding and drop-out). The evidentiary value is therefore *moderate*.

***Physical capacity and/or physical functioning***
No studies were found on the effect of manual techniques in the presence of an exacerbation on physical capacity or physical functioning.

***Future exacerbations and lung-related hospitalisation***
No studies were found on the effect of manual techniques in the presence of an exacerbation on the risk of future exacerbations or lung-related hospitalisations.

***Mortality***
No studies were found on the effect of manual techniques in the presence of an exacerbation on mortality.

***Undesirable effects***
Undesirable effects of manual therapy techniques concern a worsening of dyspnoea (*n* = 5), pain (*n* = 5), arrhythmia (*n* = 3), bronchial spasms (*n* = 1) and thoracic haematoma (*n* = 1).
The evidentiary value for dyspnoea was lowered by two levels given the limitations of the study design and execution (including blinding and drop-out) and the small number of patients (imprecision). The evidentiary value is therefore *low*.

- ***Positive expiratory pressure (PEP) in patients with a COPD exacerbation***

***Quality of life***
Osdnik (2014; *n* = 90) hardly found any effect of PEP on quality of life. The difference on the SGRQ after 8 weeks was 0.8 points (95%-CI = -6.7 to 8.3) and after six months was 1.4 points (95%-CI = -6.1 to 9.0). The evidentiary value for the quality of life was lowered by two levels given the limitations of the study design and execution and the small number of patients (imprecision). The evidentiary value is therefore *low*.

***Dyspnoea***
The effect of PEP on dyspnoea when this is measured with the mMRC is not clear. At discharge the dyspnoea was more severe after PEP (MD = 0.40; 95%-CI = -0.17 to 0.97), less severe after eight weeks (-0.40; 95%-CI = -1.02 to 0.22) and more severe again after six months 0.50 (95%-CI = -0.12 to 1.12) than in the control group patients (Osdnik 2014; *n* = 90).
The evidentiary value for dyspnoea was lowered by three levels given the limitations of the study design and execution, inconsistent results and the small number of patients (imprecision). The evidentiary value is therefore *very low*.

***Ventilation***
All patients in the Bellone (2002) study received NIV ventilation. Treatment with PEP decreased the duration of the NIV ventilation by an average of two days (MD = -2.10; 95%-CI = -2.67 to -1.53; *n* = 27; Bellone 2002). The number of patients for whom NIV was insufficient and who required invasive ventilation through endotrachial intubation was 7% lower after PEP treatment (95%-CI = -25% to 11%; *n* = 27; Bellone 2002).
However, in the Osadnik (2014) study most patients (80%) did not require ventilation. Among this less severe group of patients, PEP did not have an effect on the likelihood that the patient would require ventilation or on the duration of the ventilation.
The evidentiary value for the duration of the ventilation was lowered by three levels given the limitations of the study design and execution and the small number of patients (imprecision). The evidentiary value is therefore *low*.

***Length of hospital stay***
No difference in duration of hospitalisation (Osadnik 2014).

***Physical capacity and/or physical functioning***
The effect of PEP on physical capacity is small, inconsistent and neither clinically nor statistically significant (Osadnik 2014; *n* = 90). In the Osadnik study, the mean difference in walking distance was as follows: at discharge (MD = -26.00 m; 95%-CI = -89.53 to 37.53), after eight weeks (MD = 28.00 m; 95%-CI = -38.18 to 94.18) and after six months (MD = -4.00 m; 95%-CI = -82.39 to 74.39).
The evidentiary value for physical capacity was lowered by three levels given the limitations of the study design and execution, inconsistent results and the small number of patients (imprecision). The evidentiary value is therefore *very low*.

***Future exacerbations and lung-related hospitalisation***
The use of PEP does not decrease the risk of an exacerbation within six months (RD = -0.00; 95%-CI = -0.06 to 0.06; Osadnik 2014; *n* = 90). There is also hardly a difference in the number of lung-related hospitalisations (rehospitalisations) (RD = -0.02; 95%-CI = -0.08 to 0.04; Osadnik 2014; *n* = 90).
The evidentiary value for the risk of exacerbations and lung-related hospitalisations was lowered by three levels given the limitations of the study design and execution and the very small number of events and patients (imprecision). The evidentiary value is therefore *very low*.

***Mortality***
In the Osadnik 2014 and Bellone 2002 studies, PEP decreases the risk of dying by 5% (95%-CI = -0.16 to 0.06; *n* = 116).
The evidentiary value for mortality was lowered by three levels given the limitations of the study design and execution and the small number of events and patients (imprecision). The evidentiary value is therefore *very low*.

***Undesirable effects***
Adverse events have not been reported.

- ***PEP with oscillation (oscillating PEP, O-PEP) in patients with a COPD exacerbation***

No studies were found on the effectiveness of O-PEP on the quality of life, dyspnoea, ventilation, length of hospital stay, physical capacity or physical functioning, risk of future exacerbations or lung-related hospitalisations, mortality or other adverse events.

**Considerations**
The considerations and recommendations stem from the deliberations held in the guideline panel based on the evidence-to-decision forms. See appendix C.4.5.

**Effects** In patients with stable COPD, the PEP and O-PEP result in large to very large improvements in quality of life, dyspnoea and physical capacity. PEP has little to no effect on the risk of exacerbations or lung-related hospitalisation. O-PEP results in a slight decrease in exacerbations and a great decrease of the number of lung-related hospitalisations. The risk of undesirable effects of PEP and O-PEP is unknown. The review of the literature did not find any studies that compare breathing techniques with a control condition in patients with stable COPD.
For patients with a COPD exacerbation, breathing techniques, manual techniques and use of PEP have no or hardly any effect on the quality of life, dyspnoea, shortness of breath, length of hospital stay, ventilation, physical capacity, future exacerbations and lung-related hospitalisation. Only indications were found that breathing techniques might reduce dyspnoea during an exacerbation and that in patients with non-invasive ventilation (NIV), PEP might decrease the duration of this ventilation by two days.
**Balance between desirable and undesirable effects** Manual/passive techniques are considered to be less safe in COPD patients compared to active techniques (Ides 2011). Other undesirable effects of breathing techniques and aids are unknown.
**Value of the desirable effects** The effects quality of life, dyspnoea and exercise capacity are clinically relevant and therefore important. The number of hospitalisations and the length of hospital stay are very important, not only for the patient but also from the societal viewpoint.
The effects found differ among the study populations. Studies on the effects of mucus clearance in patients with stable COPD show positive results, while these results cannot be substantiated as well with the literature

for an exacerbation. However, it is rather unlikely from the clinical viewpoint that the effects of mucus clearance are less with an exacerbation than in a stable phase.

**Variation in value of the desirable effects** Depends on the degree of independence: The patient must be able to apply PEP and O-PEP him/herself. Required resources and variation in required resources (costs). The costs of PEP and O-PEP are less than 100 and are reimbursed by health insurance. They can be applied at home after receiving proper instruction. There are no costs associated with breathing techniques, and the patient can perform these independently.

**Cost-effectiveness** No studies.

**Acceptability** There is no reason to assume that this intervention is not acceptable. However, good therapy compliance is needed for the interventions. Acceptance of PEP and O-PEP has been investigated in the Nicolini (2018b) study with the help of a 7-point Likert scale (1 = 'very inconvenient' to 7 = 'very slightly inconvenient'). Both interventions are well accepted; there is no significant difference with the control condition in either of the two interventions (only the usual medication): PEP vs. control condition: 4.73 vs. 5.27; O-PEP vs. control condition: 4.27 vs. 5.28). No difference was found in acceptance between the devices for PEP and O-PEP.

**Feasibility** Both breathing techniques as well as PEP and O-PEP can be offered to everyone who can learn instructions and can be independently applied by patients.

Given the favourable effects, a conditional recommendation is formulated regarding the use of techniques that facilitate mucus clearance in patients with stable COPD. The recommendation is to start teaching techniques with which the patient can facilitate mucus clearance independently. When the patient has mastered this technique but cannot yet sufficiently and/or efficiently cough up the sputum (retention), use of an aid is advised. PEP or O-PEP is recommended in this case, given the demonstrated effectiveness of these aids. The preference is not to use any other techniques such as vibration, percussion or postural drainage, given that these techniques are labour-intensive and make the patient dependent on the therapist.

It is unlikely that the techniques for facilitating mucus clearance for an exacerbation have less effect for an exacerbation than for stable COPD, although the found effects are limited. That is why the same recommendations apply during an exacerbation as for stable COPD with regard to breathing techniques, aids (PEP and O-PEP) and other techniques, such as vibration, percussion or postural drainage.

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## Note C.5 Therapist supervision

### Note C.5.1 Therapy duration and frequency

#### Clinical question

**The clinical question on respiratory muscle training is divided into two sub-questions:**

- What is the optimal duration of the treatment period for COPD patients?
- What is the optimal supervision frequency during a treatment period for COPD patients?

A systematic review was conducted to answer both clinical questions*.

#### Literature about the duration of the treatment period

**Search and selection**

*Search*

The joint search of the FITT principles of exercise therapy is divided into two parts. In the first part of the search on 29 May 2018, systematic reviews (SRs) of randomised controlled studies (RCTs) were sought. This yielded 783 references. The review of Beauchamp (2011) is used to answer the sub-question about the duration of the treatment period. The search was repeated on 21 February 2019 in the PubMed, EMBASE, Web of Science, Cochrane Library, CENTRAL, EmCare, PsycINFO, ERIC and PEDro databases. Relevant search terms were used to search for new RCTs on the duration of the treatment period that were published in English or Dutch starting in 2011 (date of Beauchamp 2011 search) and randomised controlled studies on the supervision frequency. The search rationales for SRs and RCTs on exercise therapy FITT principles are listed in appendix C.5.1. The additional search yielded a total of 1,607 unique hits.

*Literature selection*

All five RCTs from the Beauchamp 2011 review were tested according to the selection criteria for this clinical question. These are included in the following table.

| *Selection criteria* | |
|---|---|
| Type of studies | SRs (search strategy 1) and RCTs (search strategy 2) |
| Type of patients | adults with COPD |
| Type of interventions | any form of exercise therapy aimed at physical capacity and/or physical activity |
| Type of comparisons | direct comparison between exercise programmes with similar content, but with a different treatment duration |
| Type of outcomes (desirable and undesirable effects) | • 'crucial outcome measures': physical capacity/exercise capacity, quality of life, dyspnoea, physical activity (activity metre)<br>• 'important outcome measures': adverse events |
| Type of timeline | immediately after the intervention |
| Other | availability of the complete text |

* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

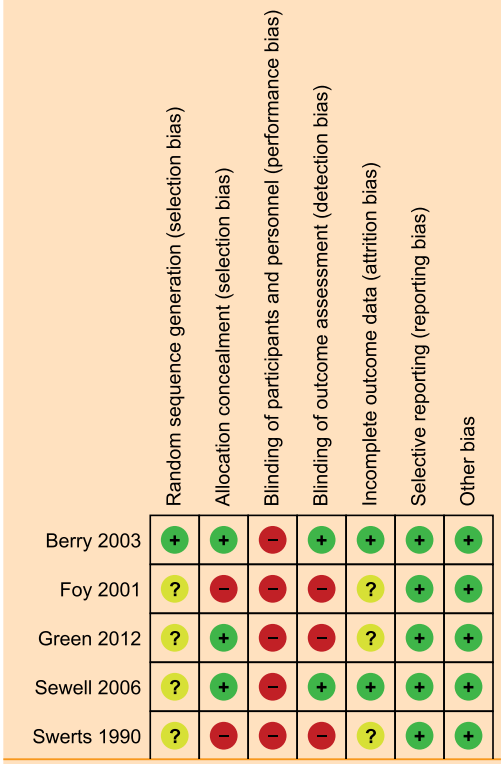
Given that all RCTs fulfilled the selection criteria, all RCTs are included. Based on the title and abstract, all studies from the additional search were excluded, due to which no additional RCTs on the duration of the treatment period were identified. The literature review on the duration of the treatment period therefore only contains five studies from the Beauchamp review. From these five studies, the results for the physical capacity, physical activity and quality of life outcome measures were extracted. The included studies do not report on adverse effects.
For the additional search on the supervision frequency, after selection based on title and abstract, the complete text of two studies was consulted, after which both studies were included. Of these two studies, the results for the physical capacity and quality of life outcome measures were extracted. The included studies do not report on physical activity (measured with an activity metre) and adverse effects

**Literature summary**

***Description of studies***
Five studies compared a short-term and long-term programme: 4 versus 7 weeks (*n* = 144, Green 2001, Sewell 2006), 8 versus 20 weeks (*n* = 27; Swerts 1990) and 6 versus 18 months (*n* = 280; Berry 2003; Foy 2001). Four studies reported on the quality of life (Berry 2003; Foy 2001; Green 2001; Sewell 2006) and four studies reported on physical capacity (Berry 2003; Green 2001; Sewell 2006; Swerts 1990). One study reported on physical activity with the help of a questionnaire (Berry 2003). However, one questionnaire is deemed unsuitable for assessing physical activity.

***Individual study quality***
The study design and execution of all five studies ('risk of bias', RoB) were assessed using the Cochrane RoB tool with low, high or unclear risk for six causes of bias, specifically random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues.
An overview of the study quality assessment (RoB) per study is provided in the following table.

***Risk of bias: Supervision duration***




\+ = yes; – = no; ? = unclear

**Results and evidentiary value**

***Favourable (effectiveness) and adverse effects (side effects)***

4 weeks versus 7 weeks

a. Quality of life. Immediately after the intervention, one study found (*n* = 44) a clinically relevant difference on the Chronic Respiratory Questionnaire (CRQ; MD = 0.61; 95%-CI = -0.15 to -1.08) in favour of the long-term programme (Green 2001). One study (*n* = 71) finds no clinically relevant difference immediately after the intervention on the CRQ between a short-term and long-term programme but does not report any data about this (Sewell 2006).
   The evidentiary value for the functional (physical) capacity outcome measure was lowered by two levels due to a limited study design and by one level due to imprecision. The evidentiary value is therefore very low.
b. Physical capacity. Immediately after the intervention, one study (*n* = 71) found a clinically relevant difference on the Endurance Shuttle Walk Test (ESWT) (MD = 124.6 sec; 95%-CI = 17 to 232.2) in favour of a longterm programme and no significant difference (no data reported) on the Incremental Shuttle Walk Test (ISWT) between a short-term and long-term programme (Sewell 2006). One study (*n* = 44) finds no clinically relevant difference immediately after the intervention on the ISWT between a short-term and long-term programme (MD -16.9 metres; 95%-CI -58.6 to 24.81) (Green 2001).
   The evidentiary value for the physical capacity outcome measure was lowered by two levels due to a limited study design and by one level due to imprecision. The evidentiary value is therefore very low.
c. Physical activity. Not reported.
d. Adverse effects: Not reported.

8 weeks versus 20 weeks

a. Quality of life. Not reported.
b. Physical capacity. One study (*n* = 26) found a small, not clinically relevant difference on the 12 Minute Walk Test (12MWT) 26 weeks after the start of the intervention (MD: 60 metres; Swerts 1990).
   The evidentiary value for the physical capacity outcome measure was lowered by two levels due to a limited study design and by one level due to imprecision. The evidentiary value is therefore very low.
c. Physical activity. Not reported.
d. Adverse effects: Not reported.

3 months versus 18 months

a. Quality of life. Immediately after the intervention, one study (*n* = 210) found a clinically relevant difference on the CRQ in the sub-domain fatigue in favour of the long-term programme, while significant but no clinically relevant differences were found between the groups in the other sub-domains (Foy 2001). One study (*n* = 140) finds a clinically relevant difference immediately after the intervention on the Fitness Arthritis and Seniors Trial functional performance inventory (FAST) between a short-term and long-term programme (Berry 2003).
   The evidentiary value for the quality of life outcome measure was lowered by two levels due to a limited study design. The evidentiary value is therefore low.
b. Physical capacity. Immediately after the intervention, one study found a small, not clinically relevant difference on the 6 Minute Walk Test (6MWT [MD: 30.5 metres]) in favour of a long-term programme (Berry 2003).
   The evidentiary value for the physical capacity outcome measure was lowered by two levels due to a limited study design and by one level due to imprecision. The evidentiary value is therefore very low.
c. Physical activity. Not reported through measurement with a activity meter. One study reported on physical activity with the help of a questionnaire. However, this is not considered to be a suitable measurement instrument.
d. Adverse effects: Not reported.

## Literature for the supervision frequency

**Search and selection**

***Search***

The joint search of the FITT principles of exercise therapy is divided into two parts. In the first part of the search on 29 May 2018, SRs of randomised controlled studies (RCTs) were sought. This yielded 783 references. No SR

was found that could be used as a basis to answer the sub-question on supervision frequency. The search was repeated on 21 February 2019 in the PubMed, EMBASE, Web of Science, Cochrane Library, CENTRAL, EmCare, PsycINFO, ERIC and PEDro databases. Relevant search terms were used to search for randomised controlled studies on supervision frequency. The additional search yielded a total of 1,607 unique hits.

*Literature selection*
For the search on supervision frequency, after selection based on title and abstract, the complete text of two studies was consulted, after which both studies were included. Of these two studies, the results for the physical capacity and quality of life outcome measures were extracted. The included studies do not report on physical activity and adverse effects.

Studies were selected based on the selection criteria in the following table.

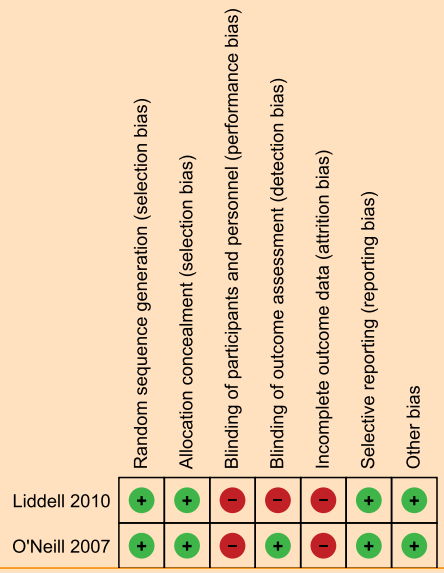
| *Selection criteria* | |
|---|---|
| Type of studies | SRs (search strategy 1) and RCTs (search strategy 2) |
| Type of patients | adults with COPD |
| Type of interventions | any form of exercise therapy aimed at physical capacity and/or physical activity |
| Type of comparisons | direct comparison between exercise programmes with similar content, but with a different supervision frequency |
| Type of outcomes (desirable and undesirable effects) | • 'crucial outcome measures': physical capacity/exercise capacity, quality of life, dyspnoea, physical activity (activity metre)<br>• 'important outcome measures': adverse events |
| Type of timeline | immediately after the intervention |
| Other | availability of the complete text |

**Literature summary**

*Description of studies*
Two studies compared 1x/week versus 2x/week supervision (Liddell 2010; O'Neill 2007). Both reported on quality of life and physical capacity.

*Individual study quality*
The study design and execution of the two studies ('risk of bias', RoB) were assessed using the Cochrane RoB tool with low, high or unclear risk for six causes of bias, specifically random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues.
An overview of the study quality assessment (RoB) per study is provided in the following table.

*Risk of bias: Supervision frequency*




\+ = yes; – = no; ? = unclear

**Results and evidentiary value**

1x/week versus 2x/week supervision

a. Quality of life. Immediately after the 8-week intervention, one study (*n* = 30) found a non-clinically relevant improvement (no MD mentioned) on the St George's Respiratory Questionnaire (SGRQ) for 2x/week supervision, while this improvement is absent for 1x/week supervision (Liddell 2010). Another study (*n* = 91) finds no clinically relevant difference immediately after the intervention on the Chronic Respiratory Disease Questionnaire (CRDQ) between 1x/week supervision and 2x/week supervision (MD = 2.54; 95% = CI-3.16 to 8.24) (O'Neill 2007). The evidentiary value for the physical capacity outcome measure was lowered by one level due to a limited study design and by one level due to imprecision. The evidentiary value is therefore low.
b. Physical capacity. One study did not find a clinically relevant difference immediately after the intervention on either the ISWT or the ESWT (no MD mentioned) between 1x/week supervision and 2x/week supervision (Liddell 2010). Another study also found no difference on either the ISWT (MD = 13.5 m; 95% = CI -10.1 to 37.2) or the ESWT (MD = 72.6 sec; 95% = CI -96.0 to 241) (O'Neill 2007).
The evidentiary value for the physical capacity outcome measure was lowered by one level due to a limited study design and by one level due to imprecision. The evidentiary value is therefore low.
c. Physical activity. Not reported.
d. Adverse effects: Not reported.

**Considerations**

The direction and strength of the recommendation are not only determined by findings in the literature. Other considerations also play a role, such as costs, acceptability and feasibility.

**Desirable effects** The systematic search identified five studies regarding treatment duration and two regarding supervision frequency. However, the evidentiary value for all outcome measures is low to very low. Both studies on supervision frequency have a low RoB (< 3 items low risk). However, the drop-out in both studies is very high (27-33%) and also selective (in particular patients with worse baseline scores). Due to the large limitations in the included studies, it is deemed undesirable to use the results of the literature review as a basis for answering both clinical questions.

**Undesirable effects** No undesirable effects were reported in the identified studies. However, when treating the physical activity and physical capacity treatable traits, insufficient supervision could lead to insufficient therapy compliance. Especially in the initial treatment phase, during which specific goals must be met, it is important to supervise patients with a high frequency. When optimising physical activity, one should start with twice per week supervision in order to promote therapy compliance. To facilitate physical capacity, pa

tients should train three times per week in order to achieve the optimal training stimuli (ACSM 2009). The pre ference is to train under full or almost full supervision, especially in the first weeks. An important reason for the training session to take place under (virtually) full supervision in the initial period is that it is very difficult for the patients themselves to estimate what the optimal training intensity is and how they should scale up the training. Intensity that is too low leads to inadequate training results, while training at an excessively high intensity increases the risk of adverse events. A frequency of two to three times per week is often maintained in training programmes in scientific studies that demonstrate the effectiveness of training pro grammes (McCarthy 2015).

A therapy duration that is too short can result in the training having an inadequate effect on the one hand and can lead to fast regression of the achieved effect on the other hand. Based on exercise physiology prin- ciples, behavioural change principles and studies on the effect of physical training in COPD patients, a period of 8–12 weeks is often maintained for the initial treatment phase, during which the aim is to achieve goals (ACSM 2009; McCarthy 2015). Sufficient attention should be paid to maintaining physical activity, because many patients can revert to their old pattern of inactivity due to insufficient supervision (Mantoani 2016, 2017). A post-treatment period is also necessary for facilitating physical capacity to ensure that the patient keeps train- ing correctly, thereby maintaining the achieved physical capacity (Jenkins 2018). This post-treatment period is also suitable for helping the patient switch to regular exercise and/or sports activities.

**Quality of desirable effects** The identified literature provides insufficient answers to the clinical questions regarding optimal supervision duration and frequency.

**Balance between desirable and undesirable effects** n/a

**Value of desirable effects** COPD patients with a mild, moderate or high symptom burden are physically limited to such an extent that an intervention for this is expected to be desirable (GOLD 2020).

**Variation in value of desirable effects** There are major differences among COPD patients. Patients with a low symptom burden are expected to attach less value to the small expected health benefits. However, patients with a high symptom burden are expected to attach a lot of value to stabilisation of physical functioning of that moment alone.

**Required resources (costs)** A high frequency and longer time period of supervision obviously results in higher direct healthcare costs than less frequent or shorter supervised therapy.

**Variation in required resources (costs)** The most vulnerable patients are expected to generate many di- recthealthcare costs because maintenance treatment is needed in order to limit deterioration of physical functioning as much as possible and/or decrease symptom burden (Jenkins 2018).

**Cost-effectiveness** Differences in cost-effectiveness between long-term and short-term and high-frequency and low-frequency supervision have not been demonstrated in scientific studies. However, more supervision in the initial treatment phase will result in a more effective scale-up of the physical activity and physical ca- pacity, thereby decreasing the risk of hospitalisation due to exacerbation. The indirect costs stemming from an exacerbation are expected to increase with a short training duration or a training frequency that is too low.

**Acceptability** To date, many COPD patients are used to exercising under the supervision of a therapist in the long term. However, it is estimated that many patients (with the exception of the most vulnerable group and patients who have undergone an interdisciplinary pulmonary rehabilitation programme) can and must tran- sition to regular exercise and/or sports activities after the initial treatment period, during which supervision by the treatment therapist is scaled down. This change will be new to many patients and therapists but will ultimately contribute to more targeted care.

**Feasibility** Based on the available literature and the previously mentioned considerations, it is not possible to determine an optimal supervision duration and frequency. However, it is possible to estimate the required number of sessions per profile, based on an intensive treatment phase and a scale-down phase. A therapist may deviate from this number if this is justified and necessary for achieving or maintaining the goal.

**Conclusion** Based on the literature and the above considerations, the guideline panel is not providing a rec- ommendation about the optimal supervision duration and frequency. However, the guideline panel is making a recommendation per profile for the maximum number of sessions that is generally required for achieving and maintaining treatment goals (Spruit 2020). The initial treatment phase is aimed at improving physical functioning based on the treatable traits. The scale-down phase is aimed at maintaining the achieved effect and facilitating self-management, so that it is possible to maintain the achieved effect without therapist supervision. Here it must be mentioned that maintenance of physical functioning without supervision is not possible for every COPD patient. Due to this the recommendation is to offer maintenance treatment to the most vulnerable group of patients and patients who have undergone an interdisciplinary pulmonary rehabilitation programme. A treatment frequency of once per week is recommended, unless this appears to be inadequate for maintaining physical functioning.

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## Note C.5.2 Group exercise therapy

### Clinical question

**When (and for whom) should you choose group training and when should you opt for individual training, and what criteria does group training need to fulfil (e.g. group size)?**

To answer the clinical question*, it was decided in consultation with the guideline panel and the review panel not to conduct a systematic review. The literature about this topic was collected in a non-systematic manner and is mentioned in the literature list below.

* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

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## Note C.6 Therapeutic actions for sub-groups

### Note C.6.1 Therapeutic actions in the presence of co-morbidity

#### Clinical question

**How are therapeutic actions defined if a COPD patient has a common co-morbidity (and takes the related medication) that impacts their physical functioning?**

To answer the clinical question*, it was decided in consultation with the guideline panel and the review panel not to conduct a systematic review. The literature about this topic was collected in a non-systematic manner and is mentioned in the literature list below.


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* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

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### Note C.6.2 Therapeutic actions in the presence of an exacerbation

#### Clinical question

**How is the therapeutic process for COPD patients with an exacerbation defined?**

To answer the clinical question, it was decided in consultation with the guideline panel and the review panel not to conduct a systematic review. The literature about this topic was collected in a non-systematic manner and is mentioned in the literature list below.

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### Note C.6.3 Therapeutic actions in the palliative phase

#### Clinical question

**How are the therapist's therapeutic actions adapted for COPD patients in the palliative phase?**

To answer the clinical question*, it was decided in consultation with the guideline panel and the review panel not to conduct a systematic review. The literature about this topic was collected in a non-systematic manner and is mentioned in the literature list below.

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* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

## Note C.7 Evaluation and conclusion of the therapeutic process

### Clinical questions

1. **After how much time are the treatment goals evaluated?**
2. **Which stop criteria are employed for ending the treatment period?**

To answer the clinical questions*, it was decided in consultation with the guideline panel and the review panel not to conduct a systematic review. The literature about this topic was collected in a non-systematic manner and is mentioned in the literature list below.

### References

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* *The recommendations for a clinical question are formulated based on the listed literature (evidence), clinical expertise and patient preferences and values (considerations).*

# Appendices

## Appendices to note C.3 'Facilitation of physical capacity'

### Appendix to C.3.1 'Endurance/interval training'

**Search rationale**

*Search string 1: COPD and FITT exercise therapy – systematic reviews; 2006 to 29 May 2018*

**PubMed** 1. COPD & oefentherapie systematische reviews (("Pulmonary Disease, Chronic Obstructive"(Mesh) OR "COPD"(tw) OR "Chronic Obstructive Pulmonary Disease"(tw) OR "Chronic Obstructive Pulmonary Diseases"(tw) OR "Chronic Obstructive Pulmonary"(tw) OR "Chronic Obstructive Lung Disease"(tw) OR "Chronic Obstructive Lung Diseases"(tw) OR "Chronic Obstructive Pulmonary"(tw) OR "COAD"(tw) OR "Chronic Obstructive Airway Disease"(tw) OR "Chronic Obstructive Airway Diseases"(tw) OR "Chronic Obstructive Airway"(tw) OR "Chronic Airflow Obstruction"(tw) OR "Chronic Airflow Obstruction"(tw) OR "Bronchitis, Chronic"(mesh) OR "Chronic Bronchitis"(tw) OR "Pulmonary Emphysema"(mesh) OR "Pulmonary Emphysema"(tw) OR "Focal Emphysema"(tw) OR "Panacinar Emphysema"(tw) OR "Panlobular Emphysema"(tw) OR "Centriacinar Emphysema"(tw) OR "Centrilobular Emphysema"(tw)) **AND** (exercis*(tw) OR "stretching"(tw) OR "Exercise Therapy"(Mesh) OR "exercise therapy"(tw) OR exercise therap*(tw) OR "Muscle Stretching Exercises"(tw) OR "Muscle Stretching Exercise"(tw) OR "Static Stretching"(tw) OR "Passive Stretching"(tw) OR "Static-Passive Stretching"(tw) OR "Static Passive Stretching"(tw) OR "Isometric Stretching"(tw) OR "Active Stretching"(tw) OR "Static-Active Stretching"(tw) OR "Static Active Stretching"(tw) OR "Ballistic Stretching"(tw) OR "Dynamic Stretching"(tw) OR "PNF Stretching"(tw) OR "Plyometric Exercise"(tw) OR "Plyometric Exercises"(tw) OR Plyometric Drill*(tw) OR "Plyometric Drills"(tw) OR "Plyometric Training"(tw) OR "Plyometric Trainings"(tw) OR "StretchShortening Exercise"(tw) OR "Stretch Shortening Exercise"(tw) OR "Stretch-Shortening Exercises"(tw) OR "Stretch-Shortening"(tw) OR "Stretch Shortening"(tw) OR "Stretch-Shortening Drills"(tw) OR "Stretch-Shortening Cycle Exercise"(tw) OR "Stretch Shortening Cycle Exercise"(tw) OR "Stretch-Shortening Cycle Exercises"(tw) OR "Resistance Training"(tw) OR "Strength Training"(tw) OR "Weight-Bearing"(tw) OR "Weight Bearing"(tw) OR "Exercise"(Mesh) OR "Exercise"(tw) OR "Exercises"(tw) OR "Physical Exercise"(tw) OR "Physical Exercises"(tw) OR "Isometric Exercises"(tw) OR "Isometric Exercise"(tw) OR "Aerobic Exercises"(tw) OR "Aerobic Exercise"(tw) OR "Circuit-Based Exercise"(tw) OR "Cool-Down Exercise"(tw) OR "Cool-Down Exercises"(tw) OR "Physical Conditioning"(tw) OR "Running"(tw) OR "Jogging"(tw) OR "Swimming"(tw) OR "Walking"(tw) OR "Warm-Up Exercise"(tw) OR "Warm-Up Exercises"(tw) OR "Physical Exertion"(Mesh) OR "Physical Exertion"(tw) OR "Physical Effort"(tw) OR "Physical Efforts"(tw) OR "Physical Fitness"(Mesh) OR "Physical Fitness"(tw) OR "Physical Endurance"(mesh) OR "Physical Endurance"(tw) OR "Anaerobic Threshold"(tw) OR "Exercise Tolerance"(tw) OR "Exercise Movement Techniques"(Mesh) OR "Exercise Movement"(tw) OR "Sports"(Mesh) OR "Sport"(tw) OR "Sports"(tw) OR "Walking"(tw) OR "Motor Activity"(Mesh) OR "Physical Activity"(tw) OR exertion*(tw) OR treadmill*(tw) OR swim*(tw) OR bicycl*(tw) OR cycling(tw) OR walk*(tw) OR muscle strength*(tw) OR "muscle training"(tw) OR "arm activity"(tw) OR "leg activity"(tw) OR fitness*(tw) OR "interval training"(tw) OR "continuous training"(tw) OR "high intensity training"(tw)) **AND** systematic(sb) **AND** ("2006/01/01"(PDAT) : "3000/12/31"(PDAT)) NOT ("Animals"(mesh) NOT "Humans"(mesh)) **AND** (english(la) OR dutch(la)) **NOT** (("Infant"(mesh) OR "Child"(mesh) OR "Adolescent"(mesh)) NOT "Adult"(mesh)))

*Search string 2: COPD and FITT exercise therapy – RCTs; 2006 to 21 February 2019*

**PubMed** (20-2-2019) COPD & oefentherapie & FITT Frequency OR Intensity OR Type OR Time/Duration & RCTs (aangepast filter) (("Pulmonary Disease, Chronic Obstructive"(mesh) OR "COPD"(tw) OR "Chronic Obstructive Pulmonary Disease"(tw) OR "Chronic Obstructive Pulmonary Diseases"(tw) OR "Chronic Obstructive Pulmonary"(tw) OR "Chronic Obstructive Lung Disease"(tw) OR "Chronic Obstructive Lung Diseases"(tw) OR "Chronic Obstructive Pulmonary"(tw) OR "COAD"(tw) OR "Chronic Obstructive Airway Disease"(tw) OR "Chronic Obstructive Airway Diseases"(tw) OR "Chronic Obstructive Airway"(tw) OR "Chronic Airflow Obstruction"(tw) OR "Chronic Airflow Obstruction"(tw) OR "Bronchitis, Chronic"(mesh) OR "Chronic Bronchitis"(tw) OR "Pulmonary Emphysema"(mesh) OR "Pulmonary Emphysema"(tw) OR "Focal Emphysema"(tw) OR "Panacinar Emphysema"(tw) OR "Panlobular Emphysema"(tw) OR "Centriacinar Emphysema"(tw) OR "Centrilobular Emphysema"(tw)) AND (exercis*(tw) OR "stretching"(tw) OR "Exercise Therapy"(Mesh) OR "exercise therapy"(tw) OR exercise therap*(tw) OR "Muscle Stretching Exercises"(tw) OR "Muscle Stretching Exercise"(tw) OR "Static Stretching"(tw) OR "Passive Stretching"(tw) OR "Static-Passive Stretching"(tw) OR "Static Passive Stretching"(tw) OR "Isometric Stretching"(tw) OR "Active Stretching"(tw) OR "Static-Active Stretching"(tw) OR "Static Active

Stretching"(tw) OR "Ballistic Stretching"(tw) OR "Dynamic Stretching"(tw) OR "PNF Stretching"(tw) OR "Plyometric Exercise"(tw) OR "Plyometric Exercises"(tw) OR Plyometric Drill*(tw) OR "Plyometric Drills"(tw) OR "Plyometric Training"(tw) OR "Plyometric Trainings"(tw) OR "Stretch-Shortening Exercise"(tw) OR "Stretch Shortening Exercise"(tw) OR "Stretch-Shortening Exercises"(tw) OR "Stretch-Shortening"(tw) OR "Stretch Shortening"(tw) OR "Stretch-Shortening Drills"(tw) OR "Stretch-Shortening Cycle Exercise"(tw) OR "Stretch Shortening Cycle Exercise"(tw) OR "Stretch-Shortening Cycle Exercises"(tw) OR "Resistance Training"(tw) OR "Strength Training"(tw) OR "Weight-Bearing"(tw) OR "Weight Bearing"(tw) OR "Exercise"(Mesh) OR "Exercise"(tw) OR "Exercises"(tw) OR "Physical Exercise"(tw) OR "Physical Exercises"(tw) OR "Isometric Exercises"(tw) OR "Isometric Exercise"(tw) OR "Aerobic Exercises"(tw) OR "Aerobic Exercise"(tw) OR "CircuitBased Exercise"(tw) OR "Cool-Down Exercise"(tw) OR "Cool-Down Exercises"(tw) OR "Physical Conditioning"(tw) OR "Running"(tw) OR "Jogging"(tw) OR "Swimming"(tw) OR "Walking"(tw) OR "Warm-Up Exercise"(tw) OR "Warm-Up Exercises"(tw) OR "Physical Exertion"(Mesh) OR "Physical Exertion"(tw) OR "Physical Effort"(tw) OR "Physical Efforts"(tw) OR "Physical Fitness"(Mesh) OR "Physical Fitness"(tw) OR "Physical Endurance"(mesh) OR "Physical Endurance"(tw) OR "Anaerobic Threshold"(tw) OR "Exercise Tolerance"(tw) OR "Exercise Movement Techniques"(Mesh) OR "Exercise Movement"(tw) OR "Sports"(Mesh) OR "Sport"(tw) OR "Sports"(tw) OR "Walking"(tw) OR "Motor Activity"(Mesh) OR "Physical Activity"(tw) OR exertion*(tw) OR treadmill*(tw) OR swim*(tw) OR bicycl*(tw) OR cycling(tw) OR walk*(tw) OR muscle strength*(tw) OR "muscle training"(tw) OR "arm activity"(tw) OR "leg activity"(tw) OR fitness*(tw) OR "interval training"(tw) OR "continuous training"(tw) OR "high intensity training"(tw)) AND ("FITT"(all fields) OR "Frequency"(tw) OR frequen*(tw) OR "per week"(tw) OR "once a week"(tw) OR "once weekly"(tw) OR "twice a week"(tw) OR "twice-weekly"(tw) OR "perweek"(tw) OR "onceaweek"(tw) OR "onceweekly"(tw) OR "twiceaweek"(tw) OR "twice-weekly"(tw) OR "three times a week"(tw) OR "thrice weekly"(tw) OR "thrice a week"(tw) OR "Intensity"(tw) OR intens*(tw) OR "Type"(tw) OR "types"(tw) OR ("muscle strength"(tw) **AND** "endurance"(tw)) OR ("muscle strength"(tw) **AND** "training"(tw)) OR ("training"(tw) AND "endurance"(tw)) OR ("training"(tw) AND "muscle strength"(tw)) OR (("ADL"(tw) OR "activities of daily living"(tw)) AND "muscle strength"(tw)) OR (("ADL" OR "activities of daily living"(tw)) AND "endurance"(tw)) OR (("ADL"(tw) OR "activities of daily living"(tw)) AND "training"(tw)) OR ("training"(tw) AND (("interval"(tw) **AND** ("endurance"(tw) OR "high Intensity"(tw) OR "continuous"(tw) OR "non-linear"(tw))) OR ("endurance"(tw) **AND** ("interval"(tw) OR "high Intensity"(tw) OR "continuous"(tw) OR "non-linear"(tw)) OR ("high Intensity"(tw) **AND** ("endurance"(tw) OR "interval"(tw) OR "continuous"(tw) OR "non-linear"(tw))) OR ("continuous"(tw) **AND** ("endurance"(tw) OR "high Intensity"(tw) OR "interval"(tw) OR "non-linear"(tw))) OR ("non-linear"(tw) **AND** ("endurance"(tw) OR "high Intensity"(tw) OR "continuous"(tw) OR "interval"(tw)))))) OR ("training"(tw) **AND** (individual*(tw) AND group*(tw))) OR "Time"(tw) OR "Time factors"(mesh) OR "Duration"(tw) OR (("criteria"(tw) OR "criterium"(tw)) **AND** ("start"(tw) OR "stop"(tw) OR "starting"(tw) OR "stopping"(tw) OR "beginning"(tw) OR "cessation"(tw) OR "ending"(tw)))) **AND** ("2006/01/01"(PDAT): "3000/12/31"(PDAT)) NOT ("Animals"(mesh) NOT "Humans"(mesh)) **AND** (english(la) OR dutch(la)) NOT (("Infant"(mesh) OR "Child"(mesh) OR "Adolescent"(mesh)) NOT "Adult"(mesh)) **AND** ("Randomized Controlled Trial"(ptyp) OR "Controlled Clinical Trial"(ptyp) OR "randomized clinical trial"(tw) OR "randomized controlled trial"(tw) OR "randomised clinical trial"(tw) OR "randomised controlled trial"(tw) OR "Random Allocation"(mesh) OR ((controlled(tiab) OR randomized(tiab) OR randomized(tiab)) **AND** (trial(tiab) OR trials(tiab))) OR "RCT"(tiab) OR "RCTs"(tiab) OR "CCT"(tiab) OR "CCTs"(tiab) OR "Control Groups"(mesh) OR "control group"(tiab) OR "Placebos"(mesh) OR "placebo"(tiab) OR "placebos"(tiab) OR "Random Allocation"(mesh) OR random*(tiab) OR "Double-Blind Method"(mesh) OR "single blind"(tiab) OR "double blind"(tiab) OR ((single(tiab) OR double(tiab) OR triple(tiab)) **AND** (blind*(tiab) OR mask*(tiab))) OR "Comparative Study"(ptyp) OR "Controlled Before-After Studies"(mesh) OR "Comparative Effectiveness Research"(mesh) OR "Cross-Over Studies"(mesh) OR "Comparative Study"(tw) OR "Controlled Before-After"(tw) OR "Comparative Effectiveness"(tw) OR "Cross-Over"(tw)))

Search strings of other databases can be requested from the KNGF.

## Appendix to C.3.3 'Hydrotherapy'

*Evidence-to-decision form for hydrotherapy for COPD patients*

| | ASSESSMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **Desirable effects** | Very small | Small | Moderate | Large | Varies | No idea | Not measured |
| **Undesirable effects** | Large | Moderate | Small | Very small | Varies | No idea | Not measured |
| **Quality of desirable effects** | Very low | Low | Acceptable | high | Varies | No idea | Not measured |
| **Balance between desirable and undesirable effects** | The undesirable effects definitely outweigh the desirable effects. | The undesirable effects definitely outweigh the desirable effects. | The desirable and undesirable effects are equal. | The desirable effects probably outweigh the undesirable effects. | The desirable effects probably outweigh the undesirable effects. | Varies | No idea | No undesirable effects measured |
| **Value of desirable effects** | Very low | Low | Acceptable | Large | No idea | | |
| **Variation in value of desirable effects** | Lots of variation | Moderate variation | Little variation | No variation | No idea | | |
| **Required resources (costs)** | High costs | Moderate costs | Virtually no costs or savings | Moderate savings | High savings | Varies | No idea |
| **Variation in required resources (costs)** | high | Moderate | Low | Very low | No idea | | |
| **Cost-effectiveness** | Not cost-effective | Probably not cost-effective | Intervention and usual care are equal | Probably cost-effective | Cost-effective | Varies | No studies available |
| **Acceptability** | Not acceptable | Probably not acceptable | Probably acceptable | Acceptable | Varies | No idea | |
| **Feasibility** | Not realistic | Probably not realistic | Probably realistic | Realistic | Varies | No idea | |

## Appendix to C.3.5 'Neuromuscular electrical stimulation'

### Search rationale

*Search string: COPD & NMES, 7 June 2018*

**PubMed** (("Pulmonary Disease, Chronic Obstructive"(Mesh) OR "COPD"(tw) OR "Chronic Obstructive Pulmonary Disease"(tw) OR "Chronic Obstructive Pulmonary Diseases"(tw) OR "Chronic Obstructive Pulmonary"(tw) OR "Chronic Obstructive Lung Disease"(tw) OR "Chronic Obstructive Lung Diseases"(tw) OR "Chronic Obstructive Pulmonary"(tw) OR "COAD"(tw) OR "Chronic Obstructive Airway Disease"(tw) OR "Chronic Obstructive Airway Diseases"(tw) OR "Chronic Obstructive Airway"(tw) OR "Chronic Airflow Obstruction"(tw) OR "Chronic Airflow Obstruction"(tw) OR "Bronchitis, Chronic"(mesh) OR "Chronic Bronchitis"(tw) OR "Pulmonary Emphysema"(mesh) OR "Pulmonary Emphysema"(tw) OR "Focal Emphysema"(tw) OR "Panacinar Emphysema"(tw) OR "Panlobular Emphysema"(tw) OR "Centriacinar Emphysema"(tw) OR "Centrilobular Emphysema"(tw)) **AND** ("Electric Stimulation Therapy"(mesh:noexp) OR "Transcutaneous Electric Nerve Stimulation"(mesh) OR "neuromuscular electrical stimulation"(tw) OR "neuromuscular electric stimulation"(tw) OR "NMES"(tw) OR "electric stimulation"(tw) OR electric stimulat*(tw) OR "electric nerve stimulation"(tw) OR electric nerve stimulat*(tw) OR (electric*(tw) **AND** stimulat*(tw)) OR "electrostimulation"(tw) OR electrostimulat*(tw) OR "electro-stimulation"(tw) OR electro-stimulat*(tw) OR (neuromusc*(tw) **AND** (electri*(tw) OR electrost*(tw)))) AND ("2015/01/01"(PDAT) : "3000/12/31"(PDAT)) NOT ("Animals"(mesh) NOT "Humans"(mesh)) AND (english(la) OR dutch(la)) NOT (("Infant"(mesh) OR "Child"(mesh) OR "Adolescent"(mesh)) NOT "Adult"(mesh)))

**Search strings of other databases can be requested from the KNGF.**

*Exclusion table for neuromuscular electrical stimulation**

| Author and year | Reason for exclusion |
|---|---|
| Giavedoni 2012 | no relevant outcome measures |
| Dolmage 2016 | no relevant outcome measures |
| Gigliotti 2004 | no data available |
| Zanotti 2010 | no data available |
| Peran 2018 | language; article in Spanish |
| Maffiuletti 2018 | study design, not an RCT but a narrative literature review |
| De Brandt 2018 | no relevant outcome measures; the systematic review is not as recent as Hill (search up to March 2015 instead of 2018) |
| Lopez-Lopez 2018 | not a good comparison: 'NMES with cardio' (I1) or 'NMES with strength' (I2) vs. 'usual care' |

** Exclusion after reading the full article.*

*Evidence-to-decision form for NMES without exercise therapy (standalone) for COPD patients*

| | ASSESSMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **Desirable effects** | Very small | Small | Moderate | Large | Varies | No idea | Not measured |
| **Undesirable effects** | Large | Moderate | Small | Very small | Varies | No idea | Not measured |
| **Quality of desirable effects** | Very low | Low | Acceptable | High | Varies | No idea | Not measured |
| **Balance between desirable and undesirable effects** | The undesirable effects definitely outweigh the desirable effects. | The undesirable effects definitely outweigh the desirable effects. | The desirable and undesirable effects are equal. | The desirable effects probably outweigh the undesirable effects. | The desirable effects probably outweigh the undesirable effects. | Varies | No idea | No undesirable effects measured |
| **Value of desirable effects** | Very low | Low | Acceptable | Large | No idea | | |
| **Variation in value of desirable effects** | Lots of variation | Moderate variation | Little variation | No variation | No idea | | |
| **Required resources (costs)** | High costs | Moderate costs | Virtually no costs or savings | Moderate savings | High savings | Varies | No idea |
| **Variation in required resources (costs)** | High | Moderate | Low | Very low | No idea | | |
| **Cost-effectiveness** | Not cost-effective | Probably not cost-effective | Intervention and usual care are equal | Probably cost-effective | Cost-effective | Varies | No studies available |
| **Acceptability** | Not acceptable | Probably not acceptable | Probably acceptable | Acceptable | Varies | No idea | |
| **Feasibility** | Not realistic | Probably not realistic | Probably realistic | Realistic | Varies | No idea | |

*Evidence-to-decision form for NMES with exercise therapy (add-on) in COPD patients*

| | ASSESSMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **Desirable effects** | Very small | Small | Moderate | Large | Varies | No idea | Not measured |
| **Undesirable effects** | Large | Moderate | Small | Very small | Varies | No idea | Not measured |
| **Quality of desirable effects** | Very low | Low | Acceptable | High | Varies | No idea | Not measured |
| **Balance between desirable and undesirable effects** | The undesirable effects definitely outweigh the desirable effects. | The undesirable effects definitely outweigh the desirable effects. | The desirable and undesirable effects are equal. | The desirable effects probably outweigh the undesirable effects. | The desirable effects probably outweigh the undesirable effects. | Varies | No idea | No undesirable effects measured |
| **Value of desirable effects** | Very low | Low | Acceptable | Large | No idea | | |
| **Variation in value of desirable effects** | Lots of variation | Moderate variation | Little variation | No variation | No idea | | |
| **Required resources (costs)** | High costs | Moderate costs | Virtually no costs or savings | Moderate savings | High savings | Varies | No idea |
| **Variation in required resources (costs)** | High | Moderate | Low | Very low | No idea | | |
| **Cost-effectiveness** | Not cost-effective | Probably not cost-effective | Intervention and usual care are equal | Probably cost-effective | Cost-effective | Varies | No studies available |
| **Acceptability** | Not acceptable | Probably not acceptable | Probably acceptable | Acceptable | Varies | No idea | |
| **Feasibility** | Not realistic | Probably not realistic | Probably realistic | Realistic | Varies | No idea | |

*Evidence-to-decision form for NMES with mobilisation in the IC and HC units in COPD patients*

| | ASSESSMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **Desirable effects** | Very small | Small | Moderate | Large | Varies | No idea | Not measured |
| **Undesirable effects** | Large | Moderate | Small | Very small | Varies | No idea | Not measured |
| **Quality of desirable effects** | Very low | Low | Acceptable | High | Varies | No idea | Not measured |
| **Balance between desirable and undesirable effects** | The undesirable effects definitely outweigh the desirable effects. | The undesirable effects definitely outweigh the desirable effects. | The desirable and undesirable effects are equal. | The desirable effects probably outweigh the undesirable effects. | The desirable effects probably outweigh the undesirable effects. | Varies | No idea | No undesirable effects measured |
| **Value of desirable effects** | Very low | Low | Acceptable | Large | No idea | | |
| **Variation in value of desirable effects** | Lots of variation | Moderate variation | Little variation | No variation | No idea | | |
| **Required resources (costs)** | High costs | Moderate costs | Virtually no costs or savings | Moderate savings | High savings | Varies | No idea |
| **Variation in required r esources (costs)** | High | Moderate | Low | Very low | No idea | | |
| **Cost-effectiveness** | Not cost-effective | Probably not cost-effective | Intervention and usual care are equal | Probably cost-effective | Cost-effective | Varies | No studies available |
| **Acceptability** | Not acceptable | Probably not acceptable | Probably acceptable | Acceptable | Varies | No idea | |
| **Feasibility** | Not realistic | Probably not realistic | Probably realistic | Realistic | Varies | No idea | |

## Appendices to note C.4 'Interventions aimed at the respiratory system'

### Appendix to C.4.1 'Respiratory muscle training'

*Evidence-to-decision form for respiratory muscle training for COPD patients*

| | ASSESSMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **Desirable effects** | Very small | Small | Moderate | Large | Varies | No idea | Not measured |
| **Undesirable effects** | Large | Moderate | Small | Very small | Varies | No idea | Not measured |
| **Quality of desirable effects** | Very low | Low | Acceptable | High | Varies | No idea | Not measured |
| **Balance between desirable and undesirable effects** | The undesirable effects definitely outweigh the desirable effects. | The undesirable effects definitely outweigh the desirable effects. | The desirable and undesirable effects are equal. | The desirable effects probably outweigh the undesirable effects. | The desirable effects probably outweigh the undesirable effects. | Varies | No idea | No undesirable effects measured |
| **Value of desirable effects** | Very low | Low | Acceptable | Large | No idea | | |
| **Variation in value of desirable effects** | Lots of variation | Moderate variation | Little variation | No variation | No idea | | |
| **Required resources (costs)** | High costs | Moderate costs | Virtually no costs or savings | Moderate savings | High savings | Varies | No idea |
| **Variation in required resources (costs)** | High | Moderate | Low | Very low | No idea | | |
| **Cost-effectiveness** | Not cost-effective | Probably not cost-effective | Intervention and usual care are equal | Probably cost-effective | Cost-effective | Varies | No studies available |
| **Acceptability** | Not acceptable | Probably not acceptable | Probably acceptable | Acceptable | Varies | No idea | |
| **Feasibility** | Not realistic | Probably not realistic | Probably realistic | Realistic | Varies | No idea | |

## Appendix to C.4.2 'Breathing techniques'

**Search rationale**

*Search string: COPD & Breathing techniques, 3 August 2008*

**PubMed** (("Pulmonary Disease, Chronic Obstructive"(Mesh) OR "COPD"(tw) OR "Chronic Obstructive Pulmonary Disease"(tw) OR "Chronic Obstructive Pulmonary Diseases"(tw) OR "Chronic Obstructive Pulmonary"(tw) OR "Chronic Obstructive Lung Disease"(tw) OR "Chronic Obstructive Lung Diseases"(tw) OR "Chronic Obstructive Pulmonary"(tw) OR "COAD"(tw) OR "Chronic Obstructive Airway Disease"(tw) OR "Chronic Obstruct,,ive Airway Diseases"(tw) OR "Chronic Obstructive Airway"(tw) OR "Chronic Airflow Obstruction"(tw) OR "Chronic Air flow Obstruction"(tw) OR "Bronchitis, Chronic"(mesh) OR "Chronic Bronchitis"(tw) OR "Pulmonary Emphysema"(mesh) OR "Pulmonary Emphysema"(tw) OR "Focal Emphysema"(tw) OR "Panacinar Emphysema"(tw) OR "Panlobular Emphysema"(tw) OR "Centriacinar Emphysema"(tw) OR "Centrilobular Emphysema"(tw)) **AND** (breath*(tw) OR "Breathing Exercises"(mesh) OR "Breathing Exercises"(tw) OR "Breathing Exercise"(tw) OR "Respiratory Muscle Training"(tw) OR "ventilation-feedback training"(tw) OR "yoga"(tw) OR "Yoga"(mesh) OR "chest physiotherapy"(tw) OR "chest physical therapy"(tw)) **AND** ("2012/01/01"(PDAT): "3000/12/31"(PDAT)) NOT ("Animals"(mesh) NOT "Humans"(mesh)) **AND** (english(la) OR dutch(la)) NOT (("Infant"(mesh) OR "Child"(mesh) OR "Adolescent"(mesh)) NOT "Adult"(mesh))) **AND** ("systematic"(sb) OR "Clinical Trial"(ptyp) OR "Clinical Trials as Topic"(mesh) OR "controlled clinical trial"(ptyp) OR "Controlled clinical Trials as Topic"(mesh) OR "clinical trial"(tiab) OR "Random Allocation"(Mesh) OR ((controlled(tiab) OR randomized(tiab) OR randomized(tiab)) **AND** (trial(tiab) OR trials(tiab))) OR RCT(tiab) OR RCTs(tiab) OR CCT(tiab) OR CCTs(tiab) OR "Control Groups"(mesh) OR "control group"(tiab) OR "placebos"(mesh) OR placebo(tiab) OR placebos(tiab) OR random*(tiab) OR "Comparative Study"(ptyp) OR "Controlled Before-After Studies"(mesh) OR "Comparative Effectiveness Research"(mesh) OR "Cross-Over Studies"(mesh) OR "Double-Blind Method"(Mesh) OR ((single(tiab) OR double(tiab) OR triple(tiab)) **AND** (blind*(tiab) OR mask*(tiab))) OR "double-blind"(tiab))

Search strings of other databases can be requested from the KNGF.

| *Exclusion table for breathing techniques** | |
|---|---|
| **Author and year** | **Reason for exclusion** |
| Araujo 2015 | study design: cross-over study |
| Bianchi 2007 | used by Holland 2012 as an additional reference but not for selection for the study |
| Borge 2014 | study design: systematic review |
| Breslin 1992 | used by Holland 2012 as an additional reference but not for selection for the study |
| Cabral 2015 | study design: cross-over study |
| Cahalin 2002 | used by Holland 2012 as an additional reference but not for selection for the study |
| Chen 2014 | incorrect outcome measures |
| Gosselink 1995 | not an RCT |
| Gosselink 2003 | used by Holland 2012 as an additional reference but not for selection for the study |
| Kaminsky 2017 | The yoga training intervention was excluded because yoga is not as relevant intervention for general therapists |

| | |
|---|---|
| Mayer 2018 | study design: systematic review with cross-over trials |
| Mendes 2018 | no control group |
| NCT01905982 2013/2018 | study still on-going, no results known yet. |
| Nicolini 2014 | incorrect intervention |
| Nicolini 2013 | incorrect intervention and complete text not available |
| Roberts 2009 | study design: systematic review, not used by Holland 2012 |
| Rocha 2015 | incorrect intervention |
| Torres-Sánchez 2017 | systematic review, one article has already been included; the other three articles do not comply with the '> 50% consists of breathing techniques' requirement |
| Van Gestel 2012 | already included in Holland 2012 |
| Vitacca 1998 | used by Holland 2012 as an additional reference but not for selection for the study |
| Yamaguti 2012 | already included in Holland 2012 |
| *Zhang 2013* | article in Chinese |
| ** Exclusion after reading the full article.* | |

*Evidence-to-decision table for pursed lip breathing for COPD patients*

| | ASSESSMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **Desirable effects** | Very small | Small | Moderate | Large | Varies | No idea | Not measured |
| **Undesirable effects** | Large | Moderate | Small | Very small | Varies | No idea | Not measured |
| **Quality of desirable effects** | Very low | Low | Acceptable | High | Varies | No idea | Not measured |
| **Balance between desirable and undesirable effects** | The undesirable effects definitely outweigh the desirable effects. | The undesirable effects definitely outweigh the desirable effects. | The desirable and undesirable effects are equal. | The desirable effects probably outweigh the undesirable effects. | The desirable effects probably outweigh the undesirable effects. | Varies | No idea | No undesirable effects measured |
| **Value of desirable effects** | Very low | Low | Acceptable | Large | No idea | | |
| **Variation in value of desirable effects** | Lots of variation | Moderate variation | Little variation | No variation | No idea | | |
| **Required resources (costs)** | High costs | Moderate costs | Virtually no costs or savings | Moderate savings | High savings | Varies | No idea |
| **Variation in required resources (costs)** | High | Moderate | Low | Very low | No idea | | |
| **Cost-effectiveness** | Not cost-effective | Probably not cost-effective | Intervention and usual care are equal | Probably cost-effective | Cost-effective | Varies | No studies available |
| **Acceptability** | Not acceptable | Probably not acceptable | Probably acceptable | Acceptable | Varies | No idea | |
| **Feasibility** | Not realistic | Probably not realistic | Probably realistic | Realistic | Varies | No idea | |

| | | | | | |
|---|---|---|---|---|---|
| **Type of recommendation** | Strong recommendation against intervention | Conditional recommendation against intervention | Conditional recommendation for intervention | Strong recommendation for intervention | |

*Evidence-to-decision form for diaphragmatic breathing for COPD patients*

| | ASSESSMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **Desirable effects** | Very small | Small | Moderate | Large | Varies | No idea | Not measured |
| **Undesirable effects** | Large | Moderate | Small | Very small | Varies | No idea | Not measured |
| **Quality of desirable effects** | Very low | Low | Acceptable | High | Varies | No idea | Not measured |
| **Balance between desirable and undesirable effects** | The adverse effects definitely outweigh the favourable effects. | The adverse effects probably outweigh the favourable effects. | The favourable and adverse effects are equal. | The favourable effects probably outweigh the adverse effects. | The favourable effects definitely outweigh the adverse effects. | Varies | No idea | No undesirable effects measured |
| **Value of desirable effects** | Very low | Low | Acceptable | Large | No idea | | |
| **Variation in value of desirable effects** | Lots of variation | Moderate variation | Little variation | No variation | No idea | | |
| **Required resources (costs)** | High costs | Moderate costs | Virtually no costs or savings | Moderate savings | High savings | Varies | No idea |
| **Variation in required resources (costs)** | High | Moderate | Low | Very low | No idea | | |
| **Cost-effectiveness** | Not cost-effective | Probably not cost-effective | Intervention and usual care are equal | Probably cost-effective | Cost-effective | Varies | No studies available |
| **Acceptability** | Not acceptable | Probably not acceptable | Probably acceptable | Acceptable | Varies | No idea | |
| **Feasibility** | Not realistic | Probably not realistic | Probably realistic | Realistic | Varies | No idea | |

| | | | | | |
|---|---|---|---|---|---|
| **Type of recommendation** | Strong recommendation against intervention | Conditional recommendation against intervention | Conditional recommendation for intervention | Strong recommendation for intervention | |

*Evidence-to-decision form for ventilation feedback for COPD patients*

| | ASSESSMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **Desirable effects** | Very small | Small | Moderate | Large | Varies | No idea | Not measured |
| **Undesirable effects** | Large | Moderate | Small | Very small | Varies | No idea | Not measured |
| **Quality of desirable effects** | Very low | Low | Acceptable | High | Varies | No idea | Not measured |
| **Balance between desirable and undesirable effects** | The adverse effects definitely outweigh the favourable effects. | The adverse effects probably outweigh the favourable effects. | The favourable and adverse effects are equal. | The favourable effects probably outweigh the adverse effects. | The favourable effects definitely outweigh the adverse effects. | Varies | No idea | No undesirable effects measured |
| **Value of desirable effects** | Very low | Low | Acceptable | Large | No idea | | |
| **Variation in value of desirable effects** | Lots of variation | Moderate variation | Little variation | No variation | No idea | | |
| **Required resources (costs)** | High costs | Moderate costs | Virtually no costs or savings | Moderate savings | High savings | Varies | No idea |
| **Variation in required resources (costs)** | High | Moderate | Low | Very low | No idea | | |
| **Cost-effectiveness** | Not cost-effective | Probably not cost-effective | Intervention and usual care are equal | Probably cost-effective | Cost-effective | Varies | No studies available |
| **Acceptability** | Not acceptable | Probably not acceptable | Probably acceptable | Acceptable | Varies | No idea | |
| **Feasibility** | Not realistic | Probably not realistic | Probably realistic | Realistic | Varies | No idea | |

| | | | | | |
|---|---|---|---|---|---|
| **Type of recommendation** | Strong recommendation against intervention | Conditional recommendation against intervention | Conditional recommendation for intervention | Strong recommendation for intervention | |

*Evidence-to-decision form for other/combined respiratory interventions for COPD patients*

| | ASSESSMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **Desirable effects** | Very small | Small | Moderate | Large | Varies | No idea | Not measured |
| **Undesirable effects** | Large | Moderate | Small | Very small | Varies | No idea | Not measured |
| **Quality of desirable effects** | Very low | Low | Acceptable | High | Varies | No idea | Not measured |
| **Balance between desirable and undesirable effects** | The adverse effects definitely outweigh the favourable effects. | The adverse effects probably outweigh the favourable effects. | The favourable and adverse effects are equal. | The favourable effects probably outweigh the adverse effects. | The favourable effects definitely outweigh the adverse effects. | Varies | No idea | No undesirable effects measured |
| **Value of desirable effects** | Very low | Low | Acceptable | Large | No idea | | |
| **Variation in value of desirable effects** | Lots of variation | Moderate variation | Little variation | No variation | No idea | | |
| **Required resources (costs)** | High costs | Moderate costs | Virtually no costs or savings | Moderate savings | High savings | Varies | No idea |
| **Variation in required resources (costs)** | High | Moderate | Low | Very low | No idea | | |
| **Cost-effectiveness** | Not cost-effective | Probably not cost-effective | Intervention and usual care are equal | Probably cost-effective | Cost-effective | Varies | No studies available |
| **Acceptability** | Not acceptable | Probably not acceptable | Probably acceptable | Acceptable | Varies | No idea | |
| **Feasibility** | Not realistic | Probably not realistic | Probably realistic | Realistic | Varies | No idea | |

| | | | | | |
|---|---|---|---|---|---|
| **Type of recommendation** | Strong recommendation against intervention | Conditional recommendation against intervention | Conditional recommendation for intervention | Strong recommendation for intervention | |

## Appendix to C.4.5 'Mucus clearance'

*Search string: COPD & mucus clearance, 3 August 2018*

**PubMed** (("Pulmonary Disease, Chronic Obstructive"(Mesh) OR "COPD"(tw) OR "Chronic Obstructive Pulmonary Disease"(tw) OR "Chronic Obstructive Pulmonary Diseases"(tw) OR "Chronic Obstructive Pulmonary"(tw) OR "Chronic Obstructive Lung Disease"(tw) OR "Chronic Obstructive Lung Diseases"(tw) OR "Chronic Obstructive Pulmonary"(tw) OR "COAD"(tw) OR "Chronic Obstructive Airway Disease"(tw) OR "Chronic Obstructive Airway Diseases"(tw) OR "Chronic Obstructive Airway"(tw) OR "Chronic Airflow Obstruction"(tw) OR "Chronic Airflow Obstruction"(tw) OR "Bronchitis, Chronic"(mesh) OR "Chronic Bronchitis"(tw) OR "Pulmonary Emphysema"(mesh) OR "Pulmonary Emphysema"(tw) OR "Focal Emphysema"(tw) OR "Panacinar Emphysema"(tw) OR "Panlobular Emphysema"(tw) OR "Centriacinar Emphysema"(tw) OR "Centrilobular Emphysema"(tw)) **AND** ("bronchopulmonary hygiene"(tw) OR "tracheobronchial clearance"(tw) OR "airway clearance"(tw) OR "airways clearance"(tw) OR "chest clearance"(tw) OR "lung clearance"(tw) OR "sputum clearance"(tw) OR "mucus clearance"(tw) OR "active cycle"(tw) OR "ACBT"(tw) OR deep breath*(tw) OR "DBE"(tw) OR "thoracic expansion"(tw) OR "TEE"(tw) OR "sustained maximal inspiration"(tw) OR "sustained maximal inspiratory"(tw) OR "SMI"(tw) OR "breathing exercise"(tw) OR "breathing exercises"(tw) OR "postural drainage"(tw) OR "gravity assisted drainage"(tw) OR "gravity-assisted drainage"(tw) OR "autogenic drainage"(tw) OR "GAD"(tw) OR "CCPT"(tw) OR "ELTGOL"(tw) OR "FET"(tw) OR "forced expiratory technique"(tw) OR huff*(tw) OR "PEP"(tw) OR "PEEP"(tw) OR "resistance breath"(tw) OR "resistance breathing"(tw) OR "positive expiratory pressure"(tw) OR "hi-PEP"(tw) OR "bubble-PEP"(tw) OR "bottle-PEP"(tw) OR "oscillating pep"(tw) OR (oscillat*(tw) **AND** "PEP"(tw)) OR "mouthpiece-PEP"(tw) OR "pari-PEP"(tw) OR "VRP1"(tw) OR "Flutter"(tw) OR "desitin"(tw) OR "cornet"(tw) OR "acapella"(tw) OR "scandipharm"(tw) OR percuss*(tw) OR vibrat*(tw) OR "vest"(tw) OR "HF-CWO"(tw) OR "OHFO"(tw) OR "chest wall oscillation"(tw) OR "chest wall oscillations"(tw) OR oral oscillat*(tw) OR thoracic oscillat*(tw) OR "Sputum/secretion"(Mesh)) **AND** ("2012/01/01"(PDAT) : "3000/12/31"(PDAT)) NOT ("Animals"(mesh) NOT "Humans"(mesh)) **AND** (english(la) OR dutch(la)) NOT (("Infant"(mesh) OR "Child"(mesh) OR "Adolescent"(mesh)) NOT "Adult"(mesh))) **AND** ("systematic"(sb) OR "Clinical Trial"(ptyp) OR "Clinical Trials as Topic"(mesh) OR "controlled clinical trial"(ptyp) OR "Controlled clinical Trials as Topic"(mesh) OR "clinical trial"(tiab) OR "Random Allocation"(Mesh) OR ((controlled(tiab) OR randomized(tiab) OR randomized(tiab)) **AND** (trial(tiab) OR trials(tiab))) OR RCT(tiab) OR RCTs(tiab) OR CCT(tiab) OR CCTs(tiab) OR "Control Groups"(mesh) OR "control group"(tiab) OR "placebos"(mesh) OR placebo(tiab) OR placebos(tiab) OR random*(tiab) OR "Comparative Study"(ptyp) OR "Controlled Before-After Studies"(mesh) OR "Comparative Effectiveness Research"(mesh) OR "Cross-Over Studies"(mesh) OR "Double-Blind Method"(Mesh) OR ((single(tiab) OR double(tiab) OR triple(-tiab)) **AND** (blind*(tiab) OR mask*(tiab))) OR "double-blind"(tiab))

**Search strings of other databases can be requested from the KNGF.**

*Exclusion table of interventions for facilitating mucus clearance in COPD patients (in the presence of stable COPD and an exacerbation)**

| Author and year | Reason for exclusion |
|---|---|
| Ambrosino 1995 | patient population unclear |
| Anthonisen 1964 | no relevant outcome measures |
| Antonaglia 2006 | no control group: IPV versus physical therapy (percussion, mobilisation and postural drainage, and ELTGOL) |
| Bateman 1979 | no clinically relevant outcome measures |
| Bateman 1981 | no clinically relevant outcome measures |
| Bellone 2000 | no control group; three interventions were directly compared to each other; no clinical outcome measures |
| Bianchi 2004 | no randomisation |
| Brown 1987 | no clinically relevant outcome measures |

| | |
|---|---|
| Campbell 1975 | no clinically relevant outcome measures |
| Cecins 1999 | patient population: no COPD but bronchiectasis |
| Cegla 2001 | no clinically relevant outcome measures |
| Cross 2010 | design article with a description of the design of the MATREX study; no outcome measures reported |
| Faager 2008 | during exercise; intervention: PLB, see C.4.2 'Breathing techniques' |
| Gass 2017 | during exercise |
| Goktalay 2013 | intervention not relevant, HFCWO is barely used in the Netherlands |
| Haidl 2002 | no clinically relevant outcome measures; note: intervention is used for a different goal: O-PEP for facilitating inhalation medication intake instead of facilitating mucus clearance |
| Hasani 1995 | P: COPD < 50% of the patient population |
| Herala 1995 | no clinically relevant outcome measures |
| Martins 2006 | no clinically relevant outcome measures; mucus clearance measured with scintigraphy with radioactive aerosol; congress abstract, no peer review |
| Martins 2007 | no clinically relevant outcome measures; only scintigraphic measurement of percentage (%) retention radioaerosol in the right lung |
| Martins 2012 | no clinically relevant outcome measures; only mucus clearance measured with scintigraphy with radioactive aerosol |
| May 1979 | no clinically relevant outcome measures; only lung |
| Morsch 2008 | P: COPD < 50% of the patient population |
| Narayanan 2014 | comparison of two different techniques (lung FT vs. mechanical percussion), no control group; no relevant outcome measures |
| Nava 2006 | no clinically relevant outcome measures |
| Newton 1978 | not a good comparison; the intervention group received different interventions (PT and IPPV); due to this, not a good comparison with the control group: it remains unclear which intervention has which effect |
| Newton 1978a | no clinically relevant outcome measures; design: cross-over without washout period |
| Nicolini 2013 | during exercise |
| Nicolini 2018b | intervention: HFCWO and IPV |
| Oldenburg 1979 | no clinically relevant outcome measures |
| Olseni 1994 | no clinically relevant outcome measures |

| | |
|---|---|
| Osadnik 2014 | no clinically relevant outcome measures; no control group; two interventions directly compared to each other |
| Padkao 2010 | during exercise |
| Pavia 1976 | no clinically relevant outcome measures; only radioaerosol clearance and sputum volume |
| Rasmussen 2001 | congress abstract, no peer review |
| Rivington-Law 1984 | no clinically relevant outcome measures |
| Russo 2016 | during exercise |
| Savci 2000 | comparison: no good comparator group: two different interventions compared to each other (autogenic drainage vs. ACBT) |
| Spahija 2005 | during exercise; intervention: PLB, see C.4.2 'Breathing techniques' |
| Su 2007 | comparison: no good control group, comparison of FET+PEP vs. PEP |
| Tang 2010 | no new RCTs found in this SR |
| Testa 2015 | intervention: IPV |
| Tiep 1986 | intervention: for PLB, see C.4.2 'Breathing techniques' |
| Van der Schans 1990 | no clinically relevant outcome measures |
| Van Hengstum 1988 | no clinically relevant outcome measures |
| Van Hengstum 1990 | no clinically relevant outcome measures |
| Van Hengstum 1991 | no clinically relevant outcome measures |
| Vargas 2005 | intervention: IPV |
| Venturelli 2012 | no clinically relevant outcome measures |
| Vishvanath 2016 | comparison: no good comparator group: two different interventions compared to each other (autogenic drainage vs. ACBT) |
| Waqas 2014 | comparison: no proper control, two different interventions compared to each other (conventional lung physical therapy with postural drainage vs. manual hyperinflation with postural drainage) |
| Wibmer 2014 | during exercise |
| Wollmer 1985 | no clinically relevant outcome measures |

** Exclusion after reading the full article.*
ACBT = active cycle of breathing technique; ELTGOL = expiration with an open glottis in the lateral posture; HFCWO = high frequency chest wall oscillation; wwIPV = intrapulmonary percussive ventilation; PLB = pursed lip breathing.

*Evidence-to-decision form for mucus clearance in the presence of stable COPD and mucus clearance*

| | ASSESSMENT | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Desirable effects** | Very small | Small | Moderate | Large | Varies | No idea | Not measured | |
| **Undesirable effects** | Large | Moderate | Small | Very small | Varies | No idea | Not measured | |
| **Quality of desirable effects** | Very low | Low | Acceptable | High | Varies | No idea | Not measured | |
| **Balance between desirable and undesirable effects** | The adverse effects definitely outweigh the favourable effects. | The adverse effects probably outweigh the favourable effects. | The favourable and adverse effects are equal. | The favourable effects probably outweigh the adverse effects. | The favourable effects definitely outweigh the adverse effects. | Varies | No idea | No undesirable effects measured |
| **Value of desirable effects** | Very low | Low | Acceptable | Large | No idea | | | |
| **Variation in value of desirable effects** | Lots of variation | Moderate variation | Little variation | No variation | No idea | | | |
| **Required resources (costs)** | High costs | Moderate costs | Virtually no costs or savings | Moderate savings | High savings | Varies | No idea | |
| **Variation in required resources (costs)** | High | Moderate | Low | Very low | No idea | | | |
| **Cost-effectiveness** | Not cost-effective | Probably not cost-effective | Intervention and usual care are equal | Probably cost-effective | Cost-effective | Varies | No studies available | |
| **Acceptability** | Not acceptable | Probably not acceptable | Probably acceptable | Acceptable | Varies | No idea | | |
| **Feasibility** | Not realistic | Probably not realistic | Probably realistic | Realistic | Varies | No idea | | |

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