**Region Västra Götaland, HTA-centrum**
Regional activity-based HTA [Verksamhetsbaserad HTA ]
Health Technology Assessment
HTA-report 2015:85

# Home mechanical ventilator treatment for chronic obstructive pulmonary disease patients with chronic hypercapnia

Becker H, Bossios A, Daxberg E, Eriksson M, Hemlin M, Jivegård L, Persson J, Svedmyr S, Sjögren P

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

# Home mechanical ventilator treatment for chronic obstructive pulmonary disease patients with chronic hypercapnia [Hemventilatorbehandling för patienter med kronisk obstruktiv lungsjukdom och kronisk hyperkapni]

Becker H[*1], Bossios A[1], Daxberg E[2], Eriksson M[2], Hemlin M[1], Jivegård L[3], Persson J[3], Svedmyr S[1], Sjögren P[3]

[1]Department of Pulmonary Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden
[2]Medical Library, Sahlgrenska University Hospital, Gothenburg, Sweden
[3]HTA-centrum, Region Västra Götaland, Gothenburg, Sweden

[*]Corresponding author

Published December 2015
2015:85
Suggested citation: Becker H, Bossios A, Daxberg E, Eriksson M, Hemlin M, Jivegård L, Persson J, Svedmyr S, Sjögren P. Home mechanical ventilator treatment for chronic obstructive pulmonary disease patients with chronic hypercapnia [Hemventilatorbehandling för patienter med kronisk obstruktiv lungsjukdom och kronisk hyperkapni]. Göteborg: Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset, HTA-centrum; 2015. Regional activity-based HTA 2015:85

## Table of contents

# 1. Abstract

**Background**
Non-invasive home ventilation (NIV) improves gas exchange and is an established treatment of alveolar hypoventilation caused by restrictive respiratory disorders. NIV is not regarded as standard treatment for hypercapnic chronic obstructive pulmonary disease (COPD) patients in the pulmonary clinic at Sahlgrenska University Hospital. Some hypercapnic COPD patients with severe nocturnal hypoxia and insomnia, who cannot use oxygen treatment, due to risk of fire associated with smoking, have been offered NIV.

**Objective**
To investigate whether NIV (high- or low-intensity) in patients with severe stable COPD (stages 3 and 4) and chronic hypercapnic respiratory failure ($PaCO_2$ ≥6.5 kPa) is better than standard treatment alone, and whether high intensity-NIV is better than low-intensity-NIV, regarding mortality, health related quality of life, sleep efficiency, hospitalisation, exacerbations, six-minute walk test (6MWT), or dyspnoea?

**Methods**
A systematic literature search was conducted in PubMed, Embase, the Cochrane Library, and a number of HTA-databases in May, 2015. At least two authors independently screened titles, abstracts and full-text articles for inclusion and extracted data.

**Main results**
The literature search identified nine RCTs, five cohort studies and five systematic reviews (SRs). The SRs were only commented upon. The RCTs had some study limitations mainly related to randomisation and blinding. The control group patients in the cohort studies were those who declined ventilator treatment due to tolerance or compliance problems, introducing a risk for selection bias. Critical and important outcomes (for decision-making) were defined as shown for PICO 1 below.

***PICO 1 - Non-invasive home ventilation compared with standard treatment***
**Critical outcomes**
Mortality data at one to two years were reported in three RCTs and three cohort studies. Mortality rate was significantly lower in the NIV group in two RCTs and one cohort study, but not in the other studies. Conclusion: Non-invasive home ventilation compared with standard treatment may slightly reduce mortality within one to two years in COPD patients with chronic hypercapnia.
Low certainty of evidence (GRADE⊕⊕◯◯).

Health related quality of life, evaluated by different questionnaires, was reported in six RCTs and one cohort study. Generic HRQoL (SF-36) in two RCTs showed conflicting results. Disease specific HRQoL scores were slightly, and significantly, improved in a majority of the studies. Conclusion: Non-invasive home ventilation compared with standard treatment may improve HRQoL assessed by disease specific questionnaires in COPD patients with chronic hypercapnia.
Low certainty of evidence (GRADE⊕⊕◯◯).

**Important outcomes**

Sleep efficiency and hospitalisation

Sleep efficiency was reported in two RCTs showing small intergroup differences. Hospitalisation was reported in three RCTs and three cohort studies. No significant differences were found in the RCTs and in one cohort study, whereas significantly fewer hospitalisations in the NIV-group were observed in two cohort studies. Conclusion: Non-invasive home ventilation compared with standard treatment may result in little or no difference in sleep efficiency and number of hospitalisations in COPD patients with chronic hypercapnia. Low certainty of evidence (GRADE⊕⊕◯◯).

Exacerbation was reported in one RCT and one cohort study with n.s. intergroup differences. Conclusion: Non-invasive home ventilation compared with standard treatment may result in little or no difference in exacerbations in COPD patients with chronic hypercapnia. Low certainty of evidence (GRADE⊕⊕◯◯).

Six minute walk-test at 3-24 months was reported in six RCTs and two cohort studies. Improved 6MWT by NIV was observed in two RCTs and one cohort study but not in the other studies. Conclusion: Non-invasive home ventilation compared with standard treatment may result in little or no difference regarding 6MWT in COPD patients with chronic hypercapnia. Low certainty of evidence (GRADE ⊕⊕◯◯).

Dyspnoea was measured in four RCTs and two cohort studies. Significant reduction of dyspnoea, at two years, in favour of NIV, was found in two RCTs, and at one year in a cohort study. Conclusion: Non-invasive home ventilation compared with standard treatment may reduce dyspnoea in COPD patients with chronic hypercapnia. Low certainty of evidence (GRADE ⊕⊕◯◯).

***PICO 2 - High intensity non-invasive home ventilation (HI-NIV) compared with low intensity non-invasive home ventilation (LI-NIV)*** was studied in one RCT (crossover study, n= 17 patients)
Mortality, hospitalisation, exacerbations were not reported.

Health related quality of life, sleep efficiency, and 6MWT

No significant intergroup differences were observed regarding health related quality of life (at six weeks), sleep efficiency (after two nights) or 6MWT (at six weeks). Conclusion: It is uncertain whether there is any difference in health related quality of life, 6MWT and sleeping efficiency, by high- compared with low-intensity non-invasive home ventilation in COPD patients with chronic hypercapnia. Very low certainty of evidence (GRADE ⊕◯◯◯).

Dyspnoea after six minute walk-test was measured by Borg Dyspnoea Scale at six weeks, with a clinically important and significant intergroup difference. Conclusion: High- compared with low-intensity non-invasive home ventilation may reduce dyspnoea in COPD patients with chronic hypercapnia. Low certainty of evidence (GRADE ⊕⊕◯◯).

**PICO 1–2: Complications** related to NIV were reported in one RCT and one cohort study. There were 4–21% mild, and no serious adverse events.

**Concluding remarks**

Non-invasive home ventilation is presently not regarded as standard treatment for hypercapnic chronic obstructive pulmonary disease (COPD) patients at the Sahlgrenska University Hospital. The present analysis suggests that NIV may slightly reduce mortality, may improve HRQoL and dyspnoea, and may result in little or no difference in sleep efficiency, hospitalisation, exacerbations and 6MWT (GRADE⊕⊕◯◯). For an estimated 23 patients the total change in cost by using NIV in hypercapnic COPD patients is estimated to 896,000 SEK during 2016. There are no serious side effects of the treatment.

## 2. Svensk sammanfattning – Swedish summary


**Bakgrund**
Icke-invasiv hemventilatorbehandling förbättrar gasutbytet och utgör en etablerad behandlingsform för alveolär hypoventilation orsakad av restriktiva lungsjukdomar. Vid Sahlgrenska Universitetssjukhusets Lungklinik är icke-invasiv hemventilatorbehandling (NIV) inte standardbehandling vid kronisk obstruktiv lungsjukdom (KOL) med kronisk hyperkapni. Vissa KOL-patienter med hyperkapni och allvarlig nattlig hypoxi med sömnlöshet, vilka inte kan erbjudas syrgas pga. brandrisk i samband med rökning, har erbjudits icke-invasiv hemventilatorbehandling.

**Syfte**
Att utvärdera huruvida icke-invasiv hemventilatorbehandling (hög- eller lågintensiv) är bättre än standardbehandling, samt huruvida högintensiv icke-invasiv hemventilatorbehandling är bättre än lågintensiv icke-invasiv hemventilatorbehandling, för patienter med allvarlig stabil KOL (stadium 3 and 4) med kronisk hyperkapnisk respiratorisk svikt ($PaCO_2$ ≥6,5 kPa), avseende mortalitet, hälsorelaterad livskvalitet, sömneffektivitet, sjukhusinläggningar, exacerbationer, sex minuters gångtest (6MWT) eller dyspné.

**Metod**
Systematisk litteratursökning gjordes i PubMed, Embase, Cochrane Library och ett antal HTA-databaser (maj 2015). Minst två av författarna läste oberoende av varandra artikeltitlar, abstrakt och fulltextartiklar för inklusion av studier och för dataextraktion.

**Sammanfattning av resultat**
Litteratursökningen identifierade nio randomiserade kontrollerade studier (RCT), fem kohortstudier och fem systematiska översikter (vilka endast kommenterades). De randomiserade studierna hade brister främst avseende randomisering och blindning. I kohortstudierna utgjordes kontrollgrupperna av patienter som hade avböjt ventilatorbehandling pga. svårigheter med följsamhet, vilket bidrog till selektionsbias. Kritiska och viktiga utfall (för beslutsfattande) definierades enligt PICO 1 (nedan).

***PICO 1 - Icke invasiv hemventilatorbehandling jämfört med standardbehandling***

**Kritiska utfall**

Mortalitet vid 1-2 år rapporterades i tre RCT och tre kohortstudier. Signifikant lägre mortalitet sågs i NIV grupperna i två RCT och i en kohort studie, men inte i de tre övriga studierna.
*Slutsats*: Icke-invasiv hemventilatorbehandling jämfört med standardbehandling kan resultera i en liten minskning avseende mortalitet efter ett till två år hos KOL-patienter med kronisk hyperkapni.
Begränsat vetenskapligt underlag (GRADE⊕⊕◯◯).

Hälsorelaterad livskvalitet (HRQoL) utifrån olika frågeformulär rapporterades i sex RCT och en kohortstudie. Resultaten från två RCT avseende generell HRQoL var motstridiga (SF-36). Sjukdomsspecifik livskvalitet förbättrades något, med statistiskt signifikant fördel för icke-invasiv hemventilatorbehandling i flertalet studier.
*Slutsats*: Icke-invasiv hemventilatorbehandling jämfört med standardbehandling kan förbättra sjukdomsspecifik HRQoL hos KOL-patienter med kronisk hyperkapni.
Begränsat vetenskapligt underlag (GRADE⊕⊕◯◯).

**Viktiga utfall**

Sömneffektivitet och sjukhusinläggningar
Sömneffektivitet rapporterades i två RCT med små skillnader mellan grupperna.
Sjukhusinläggningar studerades i tre RCT och tre kohortstudier. Tre RCT och en kohortstudie fann inga signifikanta skillnader, medan två kohortstudier redovisade signifikant färre sjukhusinläggningar för icke-invasiv hemventilatorbehandling.

*Slutsats*: Icke-invasiv hemventilatorbehandling jämfört med standardbehandling kan resultera i liten eller ingen skillnad avseende sömneffektivitet eller antalet sjukhusinläggningar hos KOL-patienter med kronisk hyperkapni. Begränsat vetenskapligt underlag (GRADE⊕⊕◯◯).

Exacerbationer rapporterades i en RCT och en kohortstudie utan signifikanta skillnader mellan grupperna.
*Slutsats*: Icke-invasiv hemventilatorbehandling jämfört med standardbehandling kan resultera i liten eller ingen skillnad avseende exacerbationer hos KOL-patienter med kronisk hyperkapni. Begränsat vetenskapligt underlag (GRADE⊕⊕◯◯).

Sex minuters gångtest (6MWT) vid 3-24 månaders uppföljning rapporterades i sex RCT och två kohortstudier. Två RCT och en kohortstudie rapporterade signifikant förbättrad 6MWT för icke-invasiv hemventilatorbehandling jämfört med standardbehandling.
*Slutsats*: Icke-invasiv hemventilatorbehandling jämfört med standardbehandling kan resultera i liten eller ingen skillnad avseende 6MWT hos KOL-patienter med kronisk hyperkapni. Begränsat vetenskapligt underlag (GRADE ⊕⊕◯◯).

Dyspné rapporterades i fyra RCT och två kohortstudier. I två RCT med två års uppföljning och i en kohortstudie med ett års uppföljning sågs signifikant reduktion av dyspné till fördel för icke-invasiv hemventilatorbehandling.
*Slutsats*: Icke invasiv hemventilatorbehandling jämfört med standardbehandling kan minska dyspné hos KOL-patienter med kronisk hyperkapni. Begränsat vetenskapligt underlag (GRADE ⊕⊕◯◯).

***PICO 2 - Högintensiv jämfört med låg intensiv icke invasiv hemventilatorbehandling*** studerades i en RCT (crossover design, n= 17 patienter).

Mortalitet, sjukhusinläggningar, exacerbationer rapporterades inte.

Hälsorelaterad livskvalitet, sömneffektivitet och sex minuters gångtest (6MWT)
Inga signifikanta skillnader sågs mellan grupperna avseende hälsorelaterad livskvalitet (efter sex veckor), sömneffektivitet (efter två nätter) eller 6MWT (efter sex veckor).
*Slutsats*: Det är osäkert huruvida hög- jämfört med lågintensiv icke-invasiv hemventilatorbehandling resulterar i någon skillnad avseende hälsorelaterad livskvalitet, sömneffektivitet eller 6MWT, hos KOL-patienter med kronisk hyperkapni. Otillräckligt vetenskapligt underlag (GRADE ⊕◯◯◯).

Dyspné efter sex minuters gångtest, enligt Borgskalan, resulterade efter sex veckor i en kliniskt betydelsefull och statistiskt signifikant skillnad till fördel för högintensiv icke-invasiv hemventilatorbehandling.
*Slutsats*: Hög- jämfört med lågintensiv icke-invasiv hemventilatorbehandling kan minska dyspné hos KOL-patienter med kronisk hyperkapni. Begränsat vetenskapligt underlag (GRADE ⊕⊕◯◯).

**PICO 1 – 2: Komplikationer** relaterade till icke invasiv hemventilatorbehandling rapporterades i en RCT och en kohortstudie, med 4–21% milda och inga allvarliga sidoeffekter.

**Sammanfattande slutsats**
Icke-invasiv hemventilatorbehandling är för närvarande inte standardbehandling för KOL-patienter med kronisk hyperkapni vid Sahlgrenska Universitetssjukhuset.
Föreliggande systematiska översikt visar att icke-invasiv hemventilatorbehandling jämfört med standardbehandling kan resultera i en liten minskning avseende mortaliteten, kan förbättra HRQoL och dyspné, och kan resultera i liten eller ingen skillnad avseende sömneffektivitet, sjukhusinläggningar, exacerbationer och 6MWT, hos KOL-patienter med kronisk hyperkapni (GRADE⊕⊕◯◯). Behandlingen är inte förknippad med några allvarliga sidoeffekter.
Den totala kostnadsökningen under 2016 skulle vara 896 000 SEK, baserat på en uppskattning med 23 patienter behandlade med icke-invasiv hemventilatorbehandling.

The above summaries were written by representatives from the HTA-centrum and approved by the Regional board for quality assurance of activity-based HTA. The Regional Health Technology Assessment Centre (HTA-centrum) Region Västra Götaland, Sweden has the task to make statements on HTA reports carried out in VGR. The English summary is a concise summary of similar outline as the summaries in the Cochrane systematic reviews. The Swedish summary addresses the question at issue, results and quality of evidence regarding efficacy and risks, and economical and ethical aspects of the particular health technology that has been assessed in the report, and is ended with a final statement/concluding remark from HTA-centrum.
Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, 2015-11-25

| | | |
|---|---|---|
| Christina Bergh | Anders Larsson | Henrik Sjövall |
| MD, Professor | MD, PhD | MD, Professor |
| Elisabeth Hansson-Olofsson | Olle Nelzén | Petteri Sjögren |
| PhD, Senior lecturer | MD, Associate professor | DDS, PhD |
| Magnus Hakeberg | Christian Rylander | Maria Skogby |
| OD, Professor | MD, PhD | RN, PhD |
| Lennart Jivegård | Ola Samuelsson | Annika Strandell |
| MD, Senior university lecturer | MD, Associate professor | MD, Associate professor |
| Jenny Kindblom | Ninni Sernert | Therese Svanberg |
| MD, Associate professor | Associate professor | HTA-librarian |

## 3. Summary of Findings (SoF-table)

**Home mechanical ventilation in chronic hypercapnic COPD patients**

| Outcomes | Number of studies per study design | Relative effect RR (95%CI) | Absolute effect | Certainty of evidence GRADE[1] |
|---|---|---|---|---|
| **PICO 1 - Non-invasive ventilation (NIV) versus standard treatment** | | | | |
| Mortality | 3 RCT<br>3 cohort | RCT: RR 0.36 to 1.06<br>Cohort: RR 0.55 to 1.23 | RCT :-0.02 to 0.21<br>Cohort: -0.05 to 0.20 | Low [2]<br>⊕⊕◯◯ |
| HRQoL | 6 RCT<br>1 cohort | Not applicable | Generic HRQoL (2 RCT):<br>1 RCT: SF-36 general health perception subscale:<br>Δ 8.6 (p=0.013, favours I)<br>1 RCT: SF-36 general health perception subscale:<br>I=20/C=32 (p=0.002, favours C), and<br>SF-36 mental health subscale:<br>I=20/C=32 (p=0.002, favours C)<br><br>Disease specific HRQoL scales (5 RCT,1 cohort):<br>Sign. and slightly improved by NIV in all studies | Low [3]<br>⊕⊕◯◯ |
| Sleep efficiency | 2 RCT | Not applicable | 1 RCT: sign. improved sleep efficiency | Low [4]<br>⊕⊕◯◯ |
| Hospitalisation | 3 RCT<br>3 cohort | Not applicable | 3 RCT: n.s.<br>2 Cohort: sign. slightly reduced in favour of NIV<br>1 cohort: n.s. | Low [5]<br>⊕⊕◯◯ |
| Exacerbation | 1 RCT<br>1 cohort | RCT: 1.0<br>cohort: 0.78 | RCT: 3 vs 3 n.s.<br>Cohort: 1.4 vs 1.8 n.s. | Low [6]<br>⊕⊕◯◯ |
| 6MWT | 6 RCT<br>2 cohort | Not applicable | 2 RCT at 24 months (6MWT):<br>Δ from -3.3 m (n.s.) to 73.3 m (p<0.001)<br>1 Cohort at 24 months (6MWT):<br>Δ > 50m, p<0.01 | Low [7]<br>⊕⊕◯◯ |
| Dyspnoea | 4 RCT<br>2 cohort | Not applicable | 2 RCT at 24 months<br>Medical Research Council score:<br>Δ from -0.4 (p<0.001) to -0.5 units (p=0.05) | Low [8]<br>⊕⊕◯◯ |
| **PICO 2 - High intensity positive pressure ventilation (HIPPV) compared with low intensity positive pressure ventilation (LIPPV)** | | | | |
| HRQoL | 1 RCT | Not applicable | At 6 weeks Severe Respiratory Insufficiency Questionnaire: Δ -0.14, n.s. | Very low [9]<br>⊕◯◯◯ |
| Sleep efficiency | 1 RCT | Not applicable | Improved sleep efficiency after two nights: Δ 4%, n.s. | Very low [10]<br>⊕◯◯◯ |
| 6MWT | 1 RCT | Not applicable | At 6 weeks (6MWT): Δ14 m, n.s. | Very low [9]<br>⊕◯◯◯ |
| Dyspnoea | 1 RCT | Not applicable | At six weeks: Δ -2.4, p=0.025 | Low [9]<br>⊕⊕◯◯ |

Footnotes: 6MWT = six-minute walk test, HRQoL = Health related quality of life, RCT = randomised controlled trial.

[1] Certainty of evidence (based on RCTs): High certainty ⊕⊕⊕⊕ = We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty ⊕⊕⊕◯ =We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty ⊕⊕◯◯ = Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty ⊕◯◯◯ = We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[2] Downgraded for inconsistency, some indirectness, some imprecision.

[3] Downgraded for some study limitations (unclear or no blinding, risk of selection bias), inconsistency, some indirectness, some imprecision.

[4] Downgraded for some study limitations (unclear or no blinding, risk of selection bias, withdrawals and dropouts), some indirectness.

[5] Downgraded for some study limitations (unclear or no blinding, risk of selection bias, withdrawals and dropouts), some indirectness and imprecision.

[6] Downgraded for study limitations (unclear or no blinding, risk of selection bias), imprecision.

[7] Downgraded for some study limitations (unclear or no blinding, risk of selection bias), some inconsistency, indirectness, imprecision.

[8] Downgraded for some study limitations (unclear or no blinding, risk of selection bias), some inconsistency, some indirectness, imprecision.

[9] Downgraded for study limitations (unclear randomisation, no blinding, risk of selection bias), imprecision.

[10] Downgraded for study limitations (unclear randomisation, no blinding, risk of selection bias), indirectness, imprecision.

## 4. Abbreviations

| | |
|---|---|
| 6MWT | Six-minute walk test |
| COPD | Chronic obstructive pulmonary disease |
| CHRF | Chronic hypercapnic respiratory failure |
| EPAP | Expiratory positive airway pressure |
| HCOPD | Hypercapnic chronic obstructive pulmonary disease |
| HIPPV | High-intensity positive pressure ventilation |
| HMV | Home mechanical ventilation |
| HRQoL | Health-related quality of life |
| HTA | Health technology assessment |
| IPAP | Inspiratory positive airway pressure |
| KOL | Kroniskt obstruktiv lungsjukdom |
| LIPPV | Low-intensity positive pressure ventilation, current standard ventilation mode for HMV |
| LTOT | Long term oxygen treatment |
| NIV | Non-invasive ventilation |
| OPD | Out-patient department |
| RCT | Randomised controlled trial |
| SR | Systematic review |
| SWEDEVOX | Swedish national register for patients on long term oxygen treatment and HMV |

# 5. Background

## Home mechanical ventilation in chronic hypercapnic patients with chronic obstructive pulmonary disease

Only a small minority of the total COPD population will develop chronic hypercapnic respiratory failure (HCOPD). In this stage of the disease the patients usually also suffer from severe hypoxia. These patients are normally prescribed long term oxygen treatment unless there are contraindications for oxygen supply.

Home mechanical ventilation (HMV) is an established treatment of alveolar hypoventilation caused by restrictive respiratory disorders, such as neuromuscular disease, rib-cage deformities and obesity. Patients treated with HMV show improved gas exchange, leading to normalization of hypercapnia, improvement of health related quality of life (HRQoL) and survival (Böing and Randerath, 2015).

However, there is no consensus whether HMV is beneficial for COPD-patients with chronic hypercapnia. During the last decades a number of studies on this topic, with different results, have been published. Interestingly, the most positive effects have been reported in a study with high inspiratory pressure (IPAP), where normalizing of hypercapnia also was accompanied with increased survival. The one-year mortality for hypercapnic COPD (HCOPD) patients without NIV is estimated as 20-22% (Anthonisen *et al*., 1986).

At the pulmonary clinic, Sahlgrenska University Hospital HMV is not regarded as a standard treatment for COPD. Some patients have been offered this treatment, for example, COPD-patients with severe nocturnal hypoxia and insomnia, who cannot use oxygen treatment due to risk of fire associated with smoking. In some of these cases HMV has been beneficial.

## Prevalence and incidence of chronic obstructive pulmonary disease with chronic hypercapnia

According to data from the SWEDEVOX register there are approximately 23 outpatients in the Gothenburg area that currently might fulfil preliminary criteria for HMV (COPD Gold III-IV with chronic $pCO_2$ > 6.5 kPa). Eight new patients are expected each year. The numbers may be slightly higher if patients who cannot use oxygen treatment (smoking is a contraindication) also would be offered HMV, or lower due to the high mortality in this group of patients.

## Present treatment of chronic obstructive pulmonary disease patients with chronic hypercapnia

In COPD, alveolar hypoventilation and hypercapnia develop in late and advanced disease. In this group of patients survival as well as HRQoL are poor.
Standard therapy includes pharmacological and non-pharmacological treatments. Pharmacological treatment has limited effect. Long term oxygen treatment may decrease mortality and morbidity, and rehabilitation programs may have some impact on exercise tolerance and HRQoL.

At present non-invasive ventilation (NIV) in HCOPD patients is mainly used in two settings: Firstly, as a short-term measure to overcome the acute decompensation in the setting of a hypercapnic exacerbation of COPD. Secondly, as a long-term measure to counteract secondary aggravation of hypercapnia due to necessary oxygen delivery, or due to coexisting obstructive sleep apnoea.
The ventilation technique used in COPD is currently consistent with the one used in other long-term NIV subgroups, i.e. low-intensity positive pressure ventilation (LIPPV).

### The normal pathway through the health care system and current wait time for medical assessment /treatment

In the Gothenburg area most COPD-patients with hypercapnia are regularly controlled at the pulmonary outpatient department at Sahlgrenska University Hospital. Some are controlled at Angered Hospital. Normally, patients with this condition would be referred to the Sleep Medicine Unit of the Department of Pulmonary Medicine, Sahlgrenska University Hospital for HMV. The current waiting time varies between one to six months depending on the severity of the patient´s condition. Some patients will start treatment during hospitalisation due to exacerbation of COPD.

### The number of patients per year who undergo home mechanical ventilation for hypercapnic chronic obstructive pulmonary disease

In the Gothenburg area, patients with HCOPD are not routinely offered MHV. In the Swedvox-register 45 patients with "lung disease" are currently treated with HMV. Probably most of these patients have COPD as the primary diagnosis; however it is unknown whether these patients also suffer from comorbidities such as sleep apnoea or restrictive respiratory disorders (e.g. obesity) as primary indication for HMV.

### Present recommendations from medical societies or health authorities

The use of HMV in COPD varies between different countries. HMV is widely recommended in the German guidelines published in 2010 (http://www.pneumologie.de/fileadmin/pneumologie/downloads/Leitlinien/1335444299103.pdf?cntmark), while in the Canadian guidelines published in 2011 it is not (McKim *et al*., 2011). The British NICE-guidelines from 2010 lie somewhere in between (http://publications.nice.org.uk/chronic-obstructive) In the Swedish national guidelines (www.ucr.uu.se/swedevox) HMV in COPD is not recommended (Swedevox). The opinions in this matter vary in different parts of Sweden. In Stockholm HMV in HCOPD is an accepted treatment option, whereas in Lund (Region Skåne) a more restrictive policy prevails.

## 6. Home mechanical ventilation

HMV can be applied either invasively (e.g. via tracheostomy) or noninvasively (e.g. via mask). Usually a ventilation mode with two different pressures is applied: a higher pressure when breathing in (IPAP) and a lower pressure (EPAP) when breathing out. Thereby, a higher tidal volume is achieved. The ventilation can be applied noninvasively via a mask over the nose or over both nose and mouth.

The technique is established in the treatment of COPD patients with acute respiratory acidosis. Usually it is called Non Invasive Positive airway Pressure Ventilation (NIPPV) in this context. It is also commonly used for the treatment of patients with chronic respiratory failure due to restrictive respiratory disorders. Then it is often referred to as "Home Mechanical Ventilation" (HMV).

## 7. Objective

**The focused question**

Is non-invasive ventilation (NIV) in patients with severe stable chronic obstructive pulmonary disease (COPD) (stages 3 and 4) and chronic hypercapnic respiratory failure (CHRF) ($PaCO_2$ ≥6.5 kPa) better than sham-NIV or standard treatment alone, and is high-intensity positive pressure ventilation (HIPPV) better than standard treatment combined with low-intensity positive pressure ventilation (LIPPV), with regard to mortality, health related quality of life, sleep efficiency*, hospitalisation, exacerbations, six-minute walk test (6MWT), or dyspnoea?

**PICO (P = Patients, I = Intervention, C = Comparison, O =Outcome)**

P = Patients with stable hypercapnic COPD ($paCO_2$ ≥6.5 kPa, stage 3 and 4)

I = Non-invasive ventilation (HIPPV or LIPPV)

C = 1. Sham-NIV or standard treatment
2. LIPPV and standard treatment

O = Outcomes

Critical for decision making:
Mortality, HRQoL (validated scales)

Important for decision making:
Sleep efficiency*, hospitalisation, exacerbation, six-minute walk test (6MWT), dyspnoea

Complications

* Sleep efficiency: a sleep ratio, the number of minutes of sleep divided by the number of minutes in bed.

# 8. Methods

## The activity based HTA-process

### Systematic literature search (Appendix 1)

During May 2015 two authors (ME, ELD) performed systematic searches in PubMed, Embase, the Cochrane Library, and a number of HTA-databases. Reference lists of relevant articles were scrutinized for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. The same two authors conducted the literature searches, selected studies, and independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all the authors, who also read the articles independently, and finally decided in a consensus meeting which articles that should be included.

### Critical appraisal and certainty of evidence

The primary publications were critically appraised using checklists modified from SBU (Swedish Council on Health Technology Assessment).
The certainty of evidence was appraised according to the Grade system (Atkins *et al*., 2004; GRADE Working group).

### Ongoing studies

A search in Clinicaltrials.gov (2015-10-09) was done using the search terms *(Chronic obstructive pulmonary disease OR Obstructive Lung Diseases OR COPD OR Chronic obstructive pulmonary disease OR COLD OR Chronic obstructive lung disease OR Chronic obstructive airway disease OR COAD) AND (Stable OR hypercapnic OR hypercapnia)) AND ((Non-invasive OR Noninvasive) AND (Ventilatory OR Ventilator OR Ventilators OR Ventilation) OR (NIV OR NPPV OR NIPPV OR Artificial respiration OR Respiration, artificial OR Positive-pressure respiration OR Intermittent positive-pressure ventilation OR Ventilation, mechanical))*
Ongoing studies, relevant for the question at issue, are listed in Section 14 (Future perspectives).

# 9. Results

### Literature search (Appendix 1)

The literature search identified a total of 1,155 articles (after removal of duplicates). Two authors (ME, ELD) excluded 1,071 articles after reading the abstracts. Another 41 articles were excluded by these authors after reading the articles in full text. The remaining 43 articles were read in full text by all authors, and 14 articles were finally included. Nine articles reported from randomised controlled trials (RCT) and five from cohort studies. They were critically appraised using checklists from SBU (Swedish Council on Health Technology Assessment). In addition, five systematic reviews (SR) were commented upon.
The included articles, with study design and patient characteristics, are presented in Appendix 2. The excluded articles, with reasons for exclusion, are listed in Appendix 3. Extracted data for each outcome and quality assessments of individual articles are summarised in Appendix 4. An overview of the results and the certainties of evidence per outcome are presented in the Summary-of-findings table (see Section 3).

### General comments regarding the included articles

Some of the included RCTs had study limitations related to randomisation and blinding. There was also imprecision and some inconsistency across studies regarding the results. The control groups in the cohort studies included mainly patients who had declined ventilator treatment due to intolerance or compliance problems. Thus, it increases the risk for selection bias. Directness was negatively affected in some studies by the inclusion of obese subjects (confounders) and patients with obstructive sleep apnoea. In some studies, a considerable proportion of patients were lost to follow up.

The effects of NIV compared with standard treatment on advanced COPD have been addressed earlier in five identified systematic reviews (SR) (Chen *et al*., 2011; COPD working group, 2012: Shi *et al.*, 2013; Struik *et al*., 2013; Brurberg and Dahm, 2014). These SRs had PICOs with different outcomes. Some of the studied outcomes were the same as in the present HTA.
Dyspnéa was improved by NIV in the two reports in which it was analysed (Chen *et al*., 2011: Struik *et al*., 2013). Struik *et al*., (2013) also reported an increased exercise tolerance after three months of NIV and Chen *et al*. (2011) found that sleep efficiency was improved by NIV. However, there were no convincing effects on mortality, quality of life or hospitalisation.

### *PICO 1 - Non-invasive ventilation compared with standard treatment*

Outcomes, critical for decision-making

**Mortality - (Appendix 4:1)**

Mortality was reported in three RCTs and three cohort studies that compared NIV with standard treatment, with 1-2 years follow-up periods.
Two RCTs and one cohort study found significantly lower mortality in the NIV group, whereas one RCT and two cohort studies failed to show significant intergroup differences.
Interestingly, the largest intergroup difference in mortality was seen in the studies with the highest ventilation pressure (one RCT and one cohort study).
Conclusion: Non-invasive home ventilation compared with standard treatment may slightly reduce mortality in chronic hypercapnic COPD patients. Low certainty of evidence (GRADE ⊕⊕◯◯).

**Health related quality of life (Appendix 4:2)**
Health related quality of life was measured in six RCTs and one cohort study, with different questionnaires in different studies. Generic HRQoL was measured in two RCTs. One RCT found a significant improvement in SF-36 general health scores by NIV (p=0.0013), whereas the other RCT (n=144) found significantly impaired SF-36 general health scores (p=0.002) and SF-36 mental health scores (0.009) in the NIV group compared with the standard care group.
Disease specific HRQoL, studied in five RCTs and one cohort study, was slightly, and significantly, improved in all of the studies.
Conclusion: Non-invasive home ventilation compared with standard treatment may improve health related quality of life as assessed by disease specific questionnaires in chronic hypercapnic COPD patients. Low certainty of evidence (GRADE ⊕⊕◯◯).

Outcomes, important for decision-making

**Sleep efficiency (Appendix 4:3)**
Sleep efficiency was reported in two RCTs. One RCT found an improvement in sleep efficiency (p=0.05) and a significant increase in total sleep time (p<0.001) by NIV compared with standard treatment.
Conclusion: Non-invasive home ventilation compared with standard treatment may result in little or no difference in sleep efficiency in chronic hypercapnic COPD patients.
Low certainty of evidence (GRADE ⊕⊕◯◯).

**Hospitalisation (Appendix 4:4)**
Hospitalisation was reported in three RCTs and three cohort studies. Three RCTs and one cohort study found no significant intergroup differences, whereas two cohort studies found significantly less hospitalisation in the NIV-group (p<0.05).
Conclusion: Non-invasive home ventilation compared with standard treatment may result in little or no difference in the number of hospitalisations in chronic hypercapnic COPD patients.
Low certainty of evidence (GRADE ⊕⊕◯◯).

**Exacerbation (Appendix 4:5)**
The number of exacerbations was reported in one RCT and one cohort study. No significant intergroup differences in exacerbation rates were found.
Conclusion: Non-invasive home ventilation compared with standard treatment may result in little or no difference in exacerbation rate in chronic hypercapnic COPD patients.
Low certainty of evidence (GRADE ⊕⊕◯◯).

**Six-minute walk test (6MWT) (Appendix 4:6)**
Six-minute walk test after three up to 24 months was reported in six RCTs and two cohort studies. Two RCTs and one cohort study reported significantly increased 6MWT results in favour of NIV.
Conclusion: Non-invasive home ventilation compared with standard treatment may result in little or no difference in 6MWT in chronic hypercapnic COPD patients.
Low certainty of evidence (GRADE ⊕⊕◯◯).

**Dyspnoea (Appendix 4:7)**
Dyspnoea was measured in four RCTs and two cohort studies that compared NIV with standard treatment. Significant reductions of dyspnoea, at two years, in favour of NIV was found in two RCTs, and at one year in one cohort study.
Conclusion: Non-invasive home ventilation compared with standard treatment may reduce dyspnoea in chronic hypercapnic COPD patients. Low certainty of evidence (GRADE ⊕⊕◯◯).

### *PICO 2 - High intensity positive pressure ventilation (HIPPV) compared with low intensity positive pressure ventilation (LIPPV)*

One randomised, crossover study including 17 patients compared HIPPV with LIPPV, with regard to HRQoL, sleep efficiency, hospitalisation, 6MWT and dyspnoea. The study had limitations related to blinding (open-label, investigators not blinded), and a short intervention period (six weeks).

Outcomes, critical for decision-making

**Mortality**
Mortality was not reported.

**Health related quality of life (HRQoL) (Appendix 4.8)**
No significant intergroup difference was found at six weeks in the disease specific (Severe Respiratory Insufficiency Questionnaire-SRI) HRQoL questionnaire, or any of its subscales.
Conclusion: It is uncertain whether there is any difference in health related quality of life by high- compared with low-intensity non-invasive home ventilation in chronic hypercapnic COPD patients. Very low certainty of evidence (GRADE ⊕◯◯◯).

Outcomes, important for decision-making

**Sleep efficiency (Appendix 4:9)**
No significant intergroup difference in sleep efficiency, as measured by polysomnography, was observed after two nights.
Conclusion: It is uncertain whether there is any difference in sleep efficiency by high- compared with low-intensity non-invasive home ventilation in chronic hypercapnic COPD patients.
Very low certainty of evidence (GRADE ⊕◯◯◯).

**Hospitalisation, exacerbation**
Hospitalisation and exacerbation were not reported in any of the studies.

**Six-minute walk test (6MWT) (Appendix 4:10)**
No significant difference in in 6MWT was found between the groups.
Conclusion: It is uncertain whether there is any difference in 6MWT by high- compared with low-intensity non-invasive home ventilation in chronic hypercapnic COPD patients.
Very low certainty of evidence (GRADE ⊕◯◯◯).

**Dyspnoea (Appendix 4:11)**
Dyspnoea, measured by Borg Dyspnoea Scale after six-minute walk test, was studied in one RCT. A clinically important and significant intergroup difference in favour of HIPPV was found at six weeks regarding exercise-related dyspnoea.
Conclusion: High- compared with low-intensity non-invasive home ventilation may reduce dyspnoea in chronic hypercapnic COPD patients. Low certainty of evidence (GRADE ⊕⊕◯◯).

**Complications (Appendix 4:12)**
Adverse events related to non-invasive home ventilation were reported in one RCT with no serious adverse events and 14% skin lesions. In one cohort study no serious adverse events, 21% skin lesions, 14% gastric distension and 14% rhinorrhoea, 7 % mucosal dryness and 4 % skin inflammation were reported.

## 10. Ethical consequences

### Ethical consequences

Since decades, NIV is standard treatment for alveolar hypoventilation secondary to restrictive lung disease. The treatment has no reported serious side effects. However, for many patients it is bothersome to start up NIV and a significant number of patients never manage to accept the treatment. This means that some patients are exposed to a demanding treatment, without being able to cope with it in the long run.

If all COPD-patients with CHRF would be offered HMV, the costs for NIV-treatment would increase markedly. If new resources are not provided, this may lead to displacement effects for the care of other patient groups.

## 11. Organisation

### Time frame for an introduction of home mechanical ventilation with high-intensity positive pressure

The infrastructure for this treatment is already available but is lacking sufficient resources.

### Present use of the home mechanical ventilation for COPD patients with CHRF in hospitals in Region Västra Götaland

HMV as such is offered at the following hospitals: Sahlgrenska University Hospital, Southern Älvsborg Hospital, Northern Älvsborg Hospital and Skaraborg Hospital. The number of COPD-patients that have been offered HMV in these hospitals is unknown. At Sahlgrenska University Hospital, 45 patients with lung disease (according to SWEDEVOX are currently treated with HMV constituting 15% of the total number receiving HMV in the Region Västra Götaland. Probably most of these patients have COPD as the primary diagnosis; however it is unknown whether these patients also suffer from comorbidities such as sleep apnea or restrictive respiratory disorders (e.g. obesity) as primary indication for HMV.

### Consequences of home mechanical ventilation with high-intensity positive pressure for personnel

It takes about three days to start up HMV treatment in a patient. This takes place either in-hospital or in the outpatient department depending on the patient's mobility. Before and after this training period a polysomnography is performed at the hospital. The follow-up scheme is individually planned, but normally the patient visits a respiratory nurse specialist for evaluation of HMV within 2-3 months, and thereafter twice during the first year after initiation of HMV. Uncomplicated cases are then followed once a year with control of blood gases and evaluation of computed data from the ventilator chip. Between scheduled visits the patient has access to specially trained staff either by telephone or by visiting the unit during drop-in consulting hours.

According to preliminary calculations based on register data (SWEDEVOX), 23 outpatients, having CHRF mainly caused by COPD, fulfil the criteria to be offered HMV in the Gothenburg area. This number is expected to increase by eight individuals each year. These patients correspond to 10-20 % of the total number of patients that are currently started on HMV per year. The estimated increase in work load would therefore be 10-20%. However, the initial work load will be higher until the prevalent patient stock has been subjected to treatment.

### Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

Very few patients on HMV from other parts of the region are treated at Sahlgrenska University Hospital. There are no reasons to believe that the number should increase in the future. However, the workload regarding technical support for the ventilator treatment will increase correspondingly.

## 12. Economic aspects

### Costs of currently used health technology

The total health care costs and the total annual health care costs are based on information from the quality register SWEDEVOX. According to the register, approximately 23 potential patients currently qualified for HMV and approximately eight potential patients per year at the Sahlgrenska University hospital in 2015. The health care cost of the currently used treatment strategies for chronic hypercapnic COPD patients ($PaCO_2$ >6.5 kPa) is estimated to be 1.17 million SEK. The total additional annual health care cost for new chronic hypercapnic COPD patients is estimated to 406,676 SEK and is based on eight patients with very severe COPD per year (Table 1).

**Table 1.** Costs for the currently used technology at Sahlgrenska University hospital, as costs per patient, total costs during 2015, and total annual costs for new cases (all costs in SEK)

| Cost units | Cost per patient GOLD IV* | Total costs during 2015 (n=23) | Total annual costs for new cases (n=8) |
|---|---|---|---|
| Drug | 13,367 | 307,430 | 106,932 |
| Hospitalisation | 31,341 | 720,832 | 250,724 |
| Outpatient care | 4,456 | 102,477 | 35,644 |
| Oxygen therapy | 1,672 | 38,456 | 13,376 |
| **Total health care costs** | **50,835** | **1,169,194** | **406,676** |

*Cost per patient in stage GOLD IV are estimated from the study by Jansson *et al.*, 2013.

### Expected costs of the new health technology

The cost of initiating the new health technology is associated with costs of the HMV of 12,000 SEK per patient (with a deprecation over 7 years, as recommended by "Landstingsförbundet" for medical technology) and accessories, such as masks and filter, with an annual cost of 2,300 SEK per patient.

During the first year, the patients are assumed to have two check-ups by a physician, and three to five check-ups by a nurse. The patients will receive HMV training of three to five times by a nurse in outpatient care. The training will be planned while the patients are hospitalised and will thereby not generate any excess cost. Before and after the training, the patients are hospitalised during one night for measurements completed by a biomedical analyst. The measurements are then assessed by a physician and documented. The cost of the HMV training range from 14,000 SEK to 18,000 SEK per patient. The highest value was used in our calculation.
Due to compliance problems, there will be a need for tighter check-ups, estimated to three by a nurse and two by a physician, in the ventilator unit. After the first year, the patients are assumed to have one to two check-ups by a nurse, and one by a physician, depending on whether complications occur. After the initial training the patients seem to manage HMV well without additional home care resources.

The total annual cost per patient initiating HMV is estimated to 39,154 SEK during the first year. After the first year, the total annual cost per patient for follow-up and accessories is estimated to 11,740 SEK (Table 2).
The costs of training the existing staff and recruiting of one new staff member (due to increasing patient numbers) were not included in the calculation.

### Total change of cost

The currently used treatment strategy for chronic hypercapnic COPD patients does not routinely include treatment with HMV. Hence, the initial costs are expected to increase for this group. The cost per patient during the first year increases to 89,989 SEK and the cost per patient after the first year increases to 62,575 SEK. The total health care costs during 2015 is estimated to 2.07 million SEK if all 23 patients receive HMV treatment. The total health care costs during 2016 are estimated to 2.16 million SEK based on the cost per patients after the first year for 23 patients and cost per patients during the first year for eight patients. Costs for HMV accounts for 583,261 SEK (27%) of the total costs during 2016 (Table 2).

**Table 2.** Costs for HMV at Sahlgrenska University hospital, as costs per patient, total costs during 2015, total annual costs for new cases, and total costs during 2016 (all costs in SEK)

| | Cost per patient during the first year | Cost per patient after first year | Total costs during 2015 (n=23) | Total annual costs for new cases (n=8) | Costs during 2016 |
|---|---|---|---|---|---|
| Total health care costs* | 50,835 | 50,835 | 1,169,194 | 406,676 | 1,575,870 |
| HMV | 39,154 | 11,740 | 900,549 | 313,234 | 583,261 |
| **Total health care costs including HMV** | **89,989** | **62,575** | **2,069,742** | **719,910** | **2,159,130** |

*Cost per patient in stage GOLD IV are estimated from the study by Jansson *et al*., 2013.

### Possibility to adopt and use the new technology within the present budget

It is possible to use the already existing local NIV service structure. However, with regards to the new patient group and the new ventilatory technique it is likely that a separate budget will be required.

### Available evidence of cost-effectiveness analyses or cost advantages or disadvantages

There are no available analyses of whether HMV is cost-effective. However, Clini *et al*. (2009), analysed the cost of care associated with domiciliary non-invasive ventilation (NIV) when added to the usual long-term oxygen therapy (LTOT) for stable hypercapnic COPD patients in Italy. The study estimated that the addition of NIV to LTOT was associated with a 20% saving of direct costs compared with LTOT alone. This was mainly caused by a lower charge due to hospitalisation during follow-up.

## 13. Discussion

The present analysis suggests that non-invasive home ventilation (NIV) compared with standard treatment may slightly reduce mortality, may improve HRQoL and dyspnoea, and may result in little or no difference in, sleep efficiency, hospitalisation, exacerbations and 6MWT (GRADE⊕⊕◯◯).

Discrepancies in results from earlier systematic reviews are probably due to differences in the studies included. Earlier reviews have not included the study of Köhnlein *et al.*, (2014) in which relatively high ventilation pressures were used. These investigators claim that the effects of NIV are linked to the effectiveness of the ventilation, measured as the decrease in $pCO_2$ that is achieved. This view may be supported by the positive effects on mortality and HQRL observed in their study. However, NIV is often not accepted by COPD-patients especially if high pressures are applied.

The difficulties to cope with NIV was reported in many of the studies. Often the control group constituted of the patients who declined NIV treatment. On the other hand, there were no serious side effects of the treatment.

## 14. Future perspective

### Scientific knowledge gaps

Systematic review of the literature performed for the current HTA revealed several unanswered questions.

There are indications that the best effects of NIV may occur when high enough pressure is applied, to significantly reduce $pCO_2$. Therefore, more studies using high pressure ventilation may be needed to fully evaluate the effects of NIV, both in the long-term and in the short-term. Also, it is important to make an attempt to characterize the criteria for responders and non-responders to NIV. Another area that has not been explicitly discussed is how the ventilation technique, and the training of patients could be improved to increase compliance.

### Ongoing research

A search in Clinicaltrials.gov (2015-10-09) identified 61 trials, eight of which were potentially relevant for our question at issue:

NCT00429156. Non-invasive Ventilation Versus Sham Ventilation in Chronic Obstructive Pulmonary Disease (COPD). An RCT of Continuation of Home Non-invasive Ventilation vs Sham Ventilation in Survivors of Acute Hypercapnic Respiratory Failure in Chronic Obstructive Pulmonary Disease. Completed – No results posted – latest update Oct 2009.

NCT01592656: Long-term Effects of Non-invasive Ventilation in Hypercapnic Chronic Obstructive Pulmonary Disease (COPD) Patients. Multicenter study - comparison of the mass flow distribution and redistribution versus the relative blood flow per lobe with functional respiratory imaging and arterial blood gas values evaluated in hypercapnic COPD patients. Terminated Oct 2013 (lack of budget) – No results posted – latest update Jan 2014.

NCT01214200: The recruitment status of this study is unknown because the information has not been verified recently. Estimated Study Completion Date: December 2012 Verified October 2012 by Philips Respironics, recruitment status was: Active, not recruiting.

NCT01526642: Home Non-invasive Ventilation for Chronic Obstructive Pulmonary Disease Patients. (Study protocol published: Lamia B, et al. Rev Mal Respir. 2012 Nov;29(9):1141-8). Status: Terminated. No study results posted.

NCT02499718: Non-invasive Positive Pressure (NPPV ) for Severe Stable Chronic Obstructive Pulmonary Disease. Recruiting. Little information available. Estimated Study Completion Date: December 2016.

NCT01120574: Home Mechanical Ventilation in Patients With Chronic Obstructive Pulmonary Disease (COPD) and Hypercapnic Response. Recruiting. Little information available. Estimated Study Completion Date: December 2015

NCT01037387: Effect of Noninvasive Ventilation on Physical Activity and Inflammation in COPD Patients. Parallel, randomised and controlled clinical trial to evaluate the effect of 12 months of noninvasive mechanical ventilation versus conventional treatment in hypercapnic patients with stable COPD. Recruiting. Estimated Study Completion Date: June 2016.

NCT01722773: Trial of Non-invasive Ventilation for Stable COPD. To study the use of NPPV in stable COPD might result in improvement in quality of life and dyspnoea. Completed. No results posted. Last updated: November 5, 2012.

After the literature search was completed a SR on NIV was published:
The cost-effectiveness of community based non-invasive ventilation (NIV) in patients with stable end stage COPD with hypercapnic respiratory failure. A systematic review and economic evaluation (Dretzke J, et al, 2015).
The study had a different PICO than the current report, including also COPD-patients without hypercapnia. However, it was suggested that HMV in a stable COPD population may be cost-effective, but the calculations were associated with uncertainty.

### Interest at the clinic/research group/organisation to start studies/trials within the research field at issue

At this time point there is no interest from our group for further research in the field.

## 15. Participants in the project.

### The question was nominated by

Mats Hemlin, MD, PhD, Department of Pulmonary Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden.

### Participants from the clinical departments

Holger Becker, MD, MRCP(UK), Department of Pulmonary Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden.
Apostolos Bossios, MD, Associate Professor, Department of Pulmonary Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden.
Mats Hemlin, MD, PhD, Department of pulmonary medicine, Sahlgrenska University Hospital, Gothenburg, Sweden.
Sven Svedmyr, MD, Department of Sleep Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden.

### Participants from the HTA-centrum

Lennart Jivegård, MD, PhD, Associate Professor, Senior University Lecturer. HTA-centrum, Region Västra Götaland, Gothenburg, Sweden.
Petteri Sjögren, DDS, PhD, HTA-centrum, Region Västra Götaland, Gothenburg, Sweden.
Josefine Persson, MSc, Health economist, HTA-centrum, Region Västra Götaland, Gothenburg, Sweden.
Eva-Lotte Daxberg, Medical Library, Sahlgrenska University Hospital, Gothenburg, Sweden.
Maud Eriksson, Medical Library, Sahlgrenska University Hospital, Gothenburg, Sweden.

### External reviewers

Sven-Erik Ricksten, Professor, MD, Department of Anaesthesia-Operation-Intensive, Sahlgrenska University Hospital, Gothenburg, Sweden.
Aso Saeed, MD, PhD, Department of Nephrology, Sahlgrenska University Hospital, Gothenburg, Sweden.

### Declaration of interest

None.

### Project time

HTA was accomplished during the period of 2015-05-18 – 2015-11-25.
Literature searches were made in May 2015.

**Appendix 1, Search strategy, study selection and references**

**Question(s) at issue:**
**The focused question**
Is non-invasive ventilation (NIV) in patients with severe stable chronic obstructive pulmonary disease (COPD) (stage 3 and 4) and chronic hypercapnic respiratory failure (CHRF) ($PaCO_2$ ≥6.5 kPa) better than sham-NIV or standard treatment alone, and is high-intensity positive pressure ventilation (HIPPV) better than standard treatment combined with low-intensity positive pressure ventilation (LIPPV), with regard to mortality, health related quality of life, sleep efficiency*, hospitalisation, exacerbations, six-minute walk test (6MWT), or dyspnoea?

PICO (P = Patients, I = Intervention, C = Comparison, O =Outcome)

P = Patients with stable hypercapnic COPD ($paCO_2$ ≥6.5 kPa, stage 3 and 4)

I = Non-invasive ventilation (HIPPV or LIPPV)

C = 1. Sham-NIV or standard treatment
2. LIPPV and standard treatment

O = Outcomes
Critical for decision making:
Mortality, HRQoL (validated scales)

Important for decision making:
Sleep efficiency*, hospitalisation, exacerbation, six-minute walk test (6MWT), dyspnoea

Complications

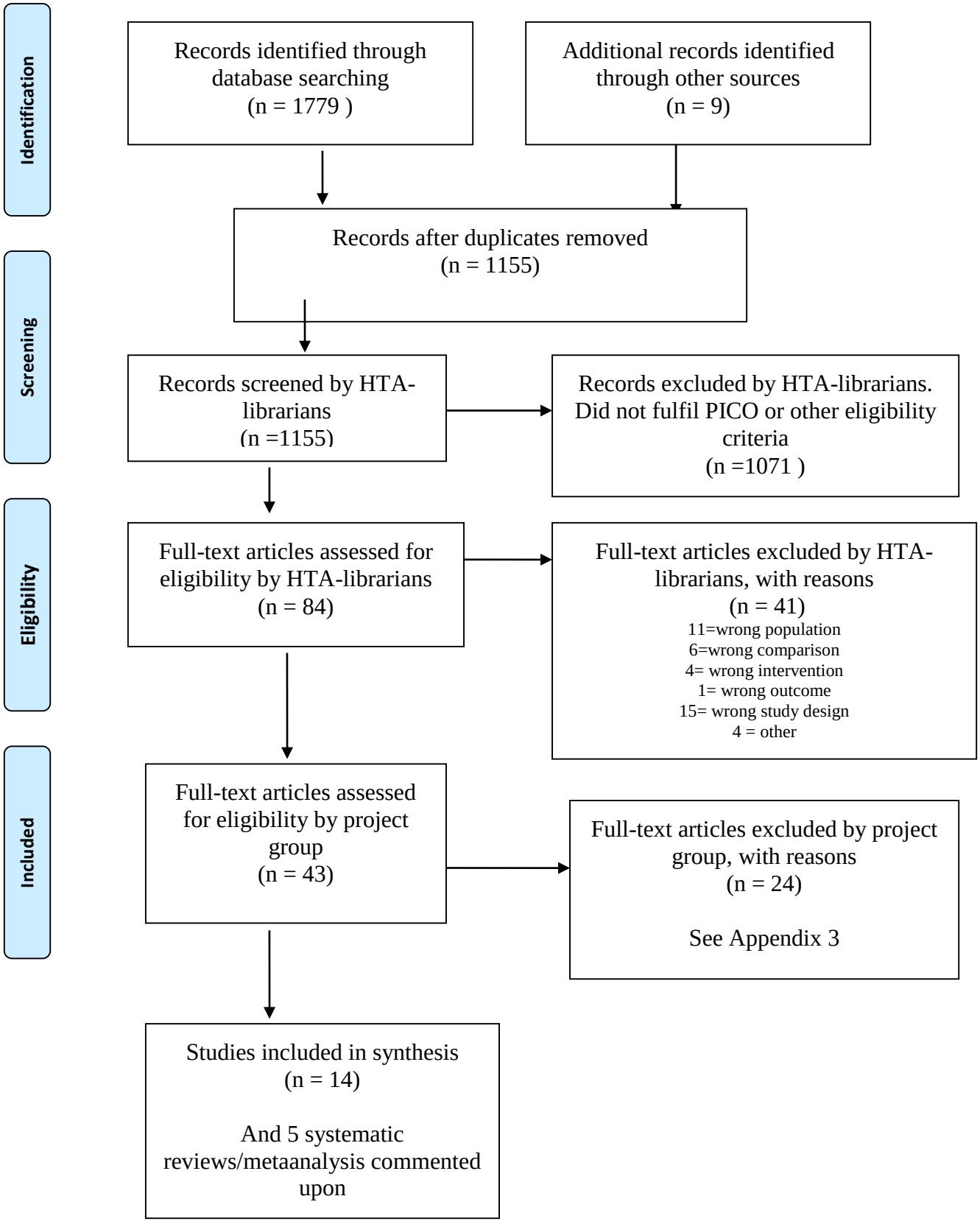
**Eligibility criteria**

**Study design:** SR, RCT, non-randomised controlled studies, case-series (n>100), for complications)

**Publikation date:** 1980-

**Language:** English, Scandinavian languages

**Selection process – flow diagram**



## Search strategies

**Database:** PubMed
**Date:** 2015-5-27
**No of results: 622 ref**

| Search | Query | Items found |
|---|---|---|
| **#12** | **Search #3 AND #6 Filters: Publication date from 1980/01/01; Danish; English; Norwegian; Swedish** | **622** |
| #7 | Search #3 AND #6 | 787 |
| #6 | Search #4 OR #5 | 65267 |
| #5 | Search Respiration, artificial[mh] OR Positive-pressure respiration[mh] OR Intermittent positive-pressure ventilation[mh] OR Ventilation, mechanical [mh] OR Artificial respiration[tiab] | 61847 |
| #4 | Search (Non-invasive[tiab] OR Noninvasive[tiab]) AND (Ventilatory[tiab] OR Ventilator[tiab] OR Ventilators[tiab] OR Ventilation[tiab]) OR NIV[tiab] OR NPPV[tiab] OR NIPPV[tiab] | 7373 |
| #3 | Search #1 AND #2 | 9535 |
| #2 | Search Stable[tiab] OR hypercapnic [tiab] OR hypercapnia[tiab] | 400554 |
| #1 | Search Pulmonary Disease, Chronic Obstructive [mh] OR Lung Diseases, Obstructive[mh] OR COPD[tiab] OR Chronic obstructive pulmonary disease[tiab] OR COLD[tiab] OR Chronic obstructive lung disease[tiab] OR Chronic obstructive airway disease[tiab] OR COAD[tiab] | 272697 |

**Database:** EMBASE (1980 to Present)
**Date:** 2015-05-27
**No of results: 873 ref**

| # | Searches | Results |
|---|---|---|
| 1 | (COPD or Chronic obstructive pulmonary disease or COLD or Chronic obstructive lung disease or Chronic obstructive airway disease or COAD).ti,ab. | 167004 |
| 2 | chronic obstructive lung disease/ or obstructive airway disease/ | 78011 |
| 3 | 1 or 2 | 197035 |
| 4 | (Stable or hypercapnic or hypercapnia).ti,ab. | 468700 |
| 5 | 3 and 4 | 9620 |
| 6 | (Non-invasive or Noninvasive).mp. and (Ventilatory or Ventilator or Ventilators or Ventilation).ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] | 10495 |
| 7 | (NIV or NPPV or NIPPV or Artificial respiration).ti,ab. | 5553 |
| 8 | exp artificial ventilation/ | 130149 |
| 9 | exp assisted ventilation/ | 112158 |

| | | |
|---|---|---|
| 10 | exp intermittent positive pressure ventilation/ | 2477 |
| 11 | positive end expiratory pressure/ | 36427 |
| 12 | exp pressure support ventilation/ | 900 |
| 13 | 6 or 7 or 8 or 9 or 10 or 11 or 12 | 183262 |
| 14 | 5 and 13 | 1419 |
| 15 | limit 14 to ((danish or english or norwegian or swedish) and yr="1980 -Current") | 1201 |
| **16** | **limit 15 to (article or conference paper or note or "review")** | **873** |

**Database:** The Cochrane Library
**Date:** 2015-05-27
**No of results: 266**

| ID | ID Search | Hits |
|---|---|---|
| #1 | COPD or "Chronic obstructive pulmonary disease" or COLD or "Chronic obstructive lung disease" or "Chronic obstructive airway disease" or COAD (Word variations have been searched) | 16425 |
| #2 | MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees | 2683 |
| #3 | MeSH descriptor: [Lung Diseases, Obstructive] explode all trees | 14211 |
| #4 | #1 or #2 or #3 | 26930 |
| #5 | stable or hypercapnic or Hypercapnia (Word variations have been searched) | 24328 |
| #6 | #4 and #5 | 2483 |
| #7 | (Non-invasive or Noninvasive) and (Ventilatory or Ventilator or Ventilators or Ventilation) (Word variations have been searched) | 1278 |
| #8 | NIV or NPPV or NIPPV or "Artificial respiration" (Word variations have been searched) | 599 |
| #9 | MeSH descriptor: [Respiration, Artificial] explode all trees | 4742 |
| #10 | MeSH descriptor: [Positive-Pressure Respiration] explode all trees | 2062 |
| #11 | MeSH descriptor: [Intermittent Positive-Pressure Ventilation] explode all trees | 195 |
| #12 | MeSH descriptor: [Respiration, Artificial] explode all trees | 4742 |
| #13 | #7 or #8 or #9 or #10 or #11 or #12 | 5670 |
| #14 | #13 and #6 Publication Year from 1980 to 2015 | **266** |

*Cochrane reviews 63*
*Other reviews 8*
*Trials: 187*
*Technology assessments 4*
*Economic evaluations 3*
*Cochrane Groups 1*

**Database:** CRD
**Date:** 2015-05-27
**No of results: 17 ref**

| | | |
|---|---|---|
| | **(COPD OR Chronic obstructive pulmonary disease OR COLD OR Chronic obstructive lung disease OR Chronic obstructive airway disease OR COAD)** | **1047** |
| 2 | MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive EXPLODE 1 | 508 |
| 3 | MeSH DESCRIPTOR Lung Diseases, Obstructive EXPLODE ALL TREES | 1294 |
| 4 | #1 OR #2 OR #3 | 1800 |
| 5 | (Stable OR hypercapnic OR hypercapnia) | 1162 |
| 6 | #4 AND #5 | 134 |
| 7 | ((Non-invasive OR Noninvasive) ) AND ((Ventilatory OR Ventilator OR Ventilators OR Ventilation) ) | 131 |
| 8 | (NIV OR NPPV OR NIPPV OR Artificial respiration) | 56 |
| 9 | MeSH DESCRIPTOR Respiration, artificial EXPLODE ALL TREES | 509 |
| 10 | MeSH DESCRIPTOR Positive-pressure respiration EXPLODE ALL TREES | 210 |
| 11 | MeSH DESCRIPTOR Intermittent positive-pressure ventilation EXPLODE ALL TREES | 8 |
| 12 | MeSH DESCRIPTOR Intermittent positive-pressure ventilation EXPLODE ALL TREES | 8 |
| 13 | (mechanical ventilation) | 391 |
| 14 | #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 | 799 |
| **15** | **#6 AND #14** | **17** |

The web-sites of **SBU, Kunnskapssenteret** and **Sundhedsstyrelsen** were visited 2015-10-19. One study, relevant to the question at issue, was found.

---

**Reference lists**
A comprehensive review of reference lists brought 9 new records.

## Reference lists

**Included studies:**

Budweiser S, Hitzl AP, Jörres RA, Heinemann F, Arzt M, Schroll S, et al. Impact of noninvasive home ventilation on long-term survival in chronic hypercapnic COPD: a prospective observational study. Int J Clin Pract. 2007a Sep; 61(9):1516-22.

Clini E, Sturani C, Porta R, Scarduelli C, Galavotti V, Vitacca M, et al. Outcome of COPD patients performing nocturnal non-invasive mechanical ventilation. Respir Med. 1998 Oct; 92(10):1215-22.

Clini E, Sturani C, Rossi A, Viaggi S, Corrado A, Donner CF, et al. Rehabilitation and Chronic Care Study Group, Italian Association of Hospital Pulmonologists (AIPO). The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. Eur Respir J. 2002 Sep; 20(3):529-38. Erratum in: Eur Respir J. 2002 Dec; 20(6):1617.

Diaz O, Begin P, Andresen M, Prieto ME, Castillo C, Jorquera J, et al. Physiological and clinical effects of diurnal noninvasive ventilation in hypercapnic COPD. Eur Respir J. 2005; 26(6):1016-23.

Dreher M, Ekkernkamp E, Walterspacher S, Walker D, Schmoor C, Storre JH, et al. Noninvasive ventilation in COPD: impact of inspiratory pressure levels on sleep quality. Chest. 2011; 140(4): 939-45.

Dreher M, Storre JH, Schmoor C, Windisch W. High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. Thorax. 2010; 65(4): 303-8.

Duiverman ML, Wempe JB, Bladder G, Jansen DF, Kerstjens HAM, Zijlstra JG, et al. Nocturnal non-invasive ventilation in addition to rehabilitation in hypercapnic patients with COPD. Thorax. 2008;63(12):1052-7.

Duiverman ML, Wempe JB, Bladder G, Vonk JM, Zijlstra JG, Kerstjens HA, et al. Two-year home-based nocturnal noninvasive ventilation added to rehabilitation in chronic obstructive pulmonary disease patients: a randomized controlled trial. Respir Res. 2011 Aug 23;12:112. doi: 10.1186/1465-9921-12-112.

Köhnlein T, Schonheit-Kenn U, Winterkamp S, Welte T, Kenn K. Noninvasive ventilation in pulmonary rehabilitation of COPD patients. Respir Med. 2009; 103(9):1329-36.

Köhnlein T, Windisch W, Köhler D, Drabik A, Geiseler J, Hartl S, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med. 2014 Sep; 2(9):698-705.

McEvoy RD, Pierce RJ, Hillman D, Esterman A, Ellis EE, Catcheside PG, et al. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. Thorax. 2009; 64(7): 561-6.

Meecham Jones DJ, Paul EA, Jones PW, Wedzicha JA. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. Am J Respir Crit Care Med. 1995 Aug; 152(2):538-44.

Paone G, Conti V, Biondi-Zoccai G, De Falco E, Chimenti I, Peruzzi M, et al. Long-term home noninvasive mechanical ventilation increases systemic inflammatory response in chronic obstructive pulmonary disease: a prospective observational study. Mediators Inflamm. 2014; 2014:503145. doi: 10.1155/2014/503145. Epub 2014 May 25. PubMed PMID: 24976687.

Tsolaki V, Pastaka C, Karetsi E, Zygoulis P, Koutsokera A, Gourgoulianis KI, et al. One-year non-invasive ventilation in chronic hypercapnic COPD: effect on quality of life. Respir Med. 2008 Jun; 102(6):904-11.

**Systematic reviews and metaanalysis only commented on**

Brurberg KG, Dahm KT. Effekt av langtids mekanisk ventilasjon (LTMV) del 3 – kols og cystisk fibrose. Rapport fra Kunnskapssenteret nr. 12−2014. Oslo: Nasjonalt kunnskapssenter for helsetjenesten, 2014.[Internet][Citerad 2015 November 03] Available at: http://www.kunnskapssenteret.no/publikasjoner/effekt-av-langtids-mekanisk-ventilasjon-ltmv-del-3-kols-og-cystisk-fibrose

Chen H, Liang BM, Xu ZB, Tang YJ, Wang K, Xiao J, et al. Long-term non-invasive positive pressure ventilation in severe stable chronic obstructive pulmonary disease: a meta-analysis. Chin Med J (Engl). 2011 Dec; 124(23):4063-70.

COPD Working Group. Noninvasive positive pressure ventilation for chronic respiratory failure patients with stable chronic obstructive pulmonary disease (COPD): an evidence-based analysis (Structured abstract). Health Technology Assessment Database [Internet]. 2012; (2). Available from: http://www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Ventilation_Chronic_March.pdf

Shi JX, Xu J, Sun WK, Su X, Zhang Y, Shi Y. Effect of noninvasive, positive pressure ventilation on patients with severe, stable chronic obstructive pulmonary disease. Chin Med J (Engl). 2013 Jan; 126(1):140-6.

Struik FM, Lacasse Y, Goldstein R, Kerstjens HM, Wijkstra PJ. Nocturnal non-invasive positive pressure ventilation for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2013 Jun 13; 6:CD002878. doi: 10.1002/14651858.CD002878.pub2.

**Excluded studies:**

Bhatt SP, Peterson MW, Wilson JS, Durairaj L. Noninvasive positive pressure ventilation in subjects with stable COPD: a randomized trial. Int J Chron Obstruct Pulmon Dis. 2013; 8:581-9.

Budweiser S, Heidtkamp F, Jorres RA, Heinemann F, Arzt M, Schroll S, et al. Predictive significance of the six-minute walk distance for long-term survival in chronic hypercapnic respiratory failure. Respiration. 2008; 75(4):418-26.

Budweiser S, Jorres RA, Riedl T, Heinemann F, Hitzl AP, Windisch W, et al. Predictors of survival in COPD patients with chronic hypercapnic respiratory failure receiving noninvasive home ventilation. Chest. 2007c; 131(6):1650-8.

Budweiser S, Jorres RA, Criee CP, Langer V, Heinemann F, Hitzl AP, et al. Prognostic value of mouth occlusion pressure in patients with chronic ventilatory failure. Respiratory Medicine. 2007b; 101(11):2343-51.

Cano NJ, Pichard C, Court-Fortune I, Costes F, Cynober L, Gérard-Boncompain M, et al. Survival of patients with chronic respiratory failure on long-term oxygen therapy and or non-invasive ventilation at home. Clin Nutr. 2015 Aug; 34(4):739-44.

Casanova C, Celli BR, Tost L, Soriano E, Abreu J, Velasco V, et al. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. Chest. 2000; 118(6): 1582-90.

Cheung AP, Chan VL, Liong JT, Lam JY, Leung WS, Lin A, et al. A pilot trial of non-invasive home ventilation after acidotic respiratory failure in chronic obstructive pulmonary disease. Int J Tuberc Lung Dis. 2010 May; 14(5):642-9.

Clini E, Vitacca M, Foglio K, Simoni P, Ambrosino N. Long-term home care programmes may reduce hospital admissions in COPD with chronic hypercapnia. Eur Respir J. 1996 Aug; 9(8):1605-10.

Clini EM, Magni G, Crisafulli E, Viaggi S, Ambrosino N. Home non-invasive mechanical ventilation and long-term oxygen therapy in stable hypercapnic chronic obstructive pulmonary disease patients: Comparison of costs. Respiration. 2009; 77(1):44-50.

De Backer L, Vos W, Dieriks B, Daems D, Verhulst S, Vinchurkar S, et al. The effects of long-term noninvasive ventilation in hypercapnic COPD patients: a randomized controlled pilot study. Int J Chron Obstruct Pulmon Dis. 2011; 6:615-24.

Dellweg D, Schonhofer B, Haidl PM, Barchfeld T, Wenzel MD, Appelhans P, et al. Short-term effect of controlled instead of assisted noninvasive ventilation in chronic respiratory failure due to chronic obstructive pulmonary disease. Respir Care. 2007 Dec; 52(12):1734-40.

Díaz O, Bégin P, Torrealba B, Jover E, Lisboa C. Effects of noninvasive ventilation on lung hyperinflation in stable hypercapnic COPD. Eur Respir J. 2002 Dec; 20(6):1490-8.

Dogan OT, Turkyilmaz S, Berk S, Epozturk K, Akkurt I. Effects of long-term non-invasive home mechanical ventilation on chronic respiratory failure. Curr Med Res Opin. 2010; 26(9):2229-36.

Garrod R, Mikelsons C, Paul EA, Wedzicha JA. Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000 Oct; 162(4 Pt 1):1335-41.

Gay PC, Hubmayr RD, Stroetz RW. Efficacy of nocturnal nasal ventilation in stable, severe chronic obstructive pulmonary disease during a 3-month controlled trial. Mayo Clin Proc. 1996 Jun; 71(6):533-42.

Lin CC. Comparison between nocturnal nasal positive pressure ventilation combined with oxygen therapy and oxygen monotherapy in patients with severe COPD. Am J Respir Crit Care Med. 1996 Aug; 154(2 Pt 1):353-8.

Lukácsovits J, Carlucci A, Hill N, Ceriana P, Pisani L, Schreiber A, et al. Physiological changes during low- and high-intensity noninvasive ventilation. Eur Respir J. 2012 Apr; 39(4):869-75.

Murphy PB, Brignall K, Moxham J, Polkey MI, Davidson AC, Hart N. High pressure versus high intensity noninvasive ventilation in stable hypercapnic chronic obstructive pulmonary disease: a randomized crossover trial. Int J Chron Obstruct Pulmon Dis. 2012; 7:811-8.

Sin DD, Wong E, Mayers I, Lien DC, Feeny D, Cheung H, et al. Effects of nocturnal noninvasive mechanical ventilation on heart rate variability of patients with advanced COPD. Chest. 2007;131(1):156-63.

Struik FM, Lacasse Y, Goldstein RS, Kerstjens HA, Wijkstra PJ. Nocturnal noninvasive positive pressure ventilation in stable COPD: a systematic review and individual patient data meta-analysis. Respir Med. 2014b Feb; 108(2):329-37.

Struik FM, Sprooten RTM, Kerstjens HAM, Bladder G, Zijnen M, Sin JA, et al. Nocturnal non-invasive ventilation in copd patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: A randomised, controlled, parallel-group study. Thorax. 2014a; 69(9):826-34.

Strumpf DA, Millman RP, Carlisle CC, Grattan LM, Ryan SM, Erickson AD, et al. Nocturnal positive-pressure ventilation via nasal mask in patients with severe chronic obstructive pulmonary disease. Am Rev Respir Dis. 1991 Dec; 144(6):1234-9.

Tuggey JM, Plant PK, Elliott MW. Domiciliary non-invasive ventilation for recurrent acidotic exacerbations of COPD: An economic analysis. Thorax. 2003; 58(10):867-71.

Windisch W, Dreher M, Storre JH, Sorichter S. Nocturnal non-invasive positive pressure ventilation: physiological effects on spontaneous breathing. Respir Physiol Neurobiol. 2006 Feb 28; 150(2-3):251-60.

**Other references:**

Anthonisen NR, Wright EC, Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. Am Rev Respir Dis. 1986 Jan;133(1):14-20.

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19; 328(7454):1490-4.

Böing S, Randerath WJ. Chronic hypoventilation syndromes and sleep-related hypoventilation. J Thorac Dis. 2015 Aug;7(8):1273-85.

[Checklist from SBU regarding cohort studies]. [Internet]. [cited 2015 October 19] Available from: https://www2.sahlgrenska.se/upload/SU/HTA-centrum/Hj%c3%a4lpmedel%20under%20projektet/B03_Granskningsmall%20f%c3%b6r%20kohortstudier%20med%20kontrollgrupp%202014-10-29.doc

Dretzke J, Blissett D, Dave C, Mukherjee R, Price M, Bayliss S, et al. The cost-effectiveness of domiciliary non-invasive ventilation in patients with end-stage chronic obstructive pulmonary disease: a systematic review and economic evaluation. Health Technol Assess 2015;19(81).[Internet]. [cited 2015 November 2015]. Available from: http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0007/154753/FullReport-hta19810.pdf

[Checklists from SBU regarding randomized controlled trials. [Internet]. [cited 2015 October 19] Available from: https://www2.sahlgrenska.se/upload/SU/HTA-centrum/Hj%c3%a4lpmedel%20under%20projektet/B02_Granskningsmall%20f%c3%b6r%20%20randomiserad%20kontrollerad%20pr%c3%b6vning%20RCT%202014-10-29.doc

GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19; 328(7454):1490-4.

GRADE Working Group. List of GRADE working group publications and grants [Internet]. [Place unknown]: GRADE Working Group, c2005-2009 [cited 2015 October 19]. Available from: http://www.gradeworkinggroup.org/publications/index.htm

Jansson SA, Backman H, Stenling A, Lindberg A, Rönmark E, Lundbäck B. Health economic costs of COPD in Sweden by disease severity--has it changed during a ten years period? Respir Med. 2013 Dec; 107(12):1931-8.

McKim DA, Road J, Avendano M, Abdool S, Cote F, Duguid N, et al. Canadian Thoracic Society Home Mechanical Ventilation Committee. Home mechanical ventilation: a Canadian Thoracic Society clinical practice guideline. Can Respir J. 2011 Jul-Aug; 18(4):197-215.

Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21; 6(7):e1000097.

NICE. National Institute for Health and Care Excellence (2010). Chronic obstructive pulmonary disease in over 16s: diagnosis and management**.** [NICE guidelines [CG101]. [Internet]. (Cited 2015 November 02]. Available from: (http://publications.nice.org.uk/chronic-obstructive pulmonary disease-cg101)

Windisch W, Walterspacher S, Siemon K, Geiseler J, Sitter H; German Society for Pneumology. Guidelines for non-invasive and invasive mechanical ventilation for treatment of chronic respiratory failure. Published by the German Society for Pneumology (DGP). Pneumologie. 2010 Oct; 64(10):640-52.

Swedevox. Riktlinjer LTMV i hemmet: andningssviktregistret Swedevox. Nationellt kvalitetsregister för långtidsbehandling med oxygen (LTOT), respirator (LTMV) eller CPAP[Internet]. [Cited 2015 November 02]. Available at: file:///C:/Users/evada14/Downloads/Riktlinjer%20respirator%20i%20hemmet%202013.pdf

**Appendix 2 – Included studies – design and patient characteristics.**

| Author, year, | Country | Study Design | No of participants (mean age, years) | Follow up period (SD) | % men | Intervention vs comparison (PICO 1, 2, 3) | Outcomes |
|---|---|---|---|---|---|---|---|
| Clini, 2002 | Italy | Multicentre prospective randomised controlled study | n=90<br>65 years | 2 years | 80 | PICO 1 | SO: mortality, QOL, sleep quality, hospitalisation, 6MWT, dyspnea |
| Diaz, 2005 | Chile | Randomised controlled study | n=42<br>67 years | 3 weeks | 86 | PICO 1 | O: 6MWT, dyspnea |
| Dreher, 2010 | Germany | Randomised controlled crossover study | n=17<br>not reported | 6 weeks | 69 | PICO 2 | SO: QOL, 6MWT, dyspnea |
| Dreher, 2011 | Germany | Randomised controlled crossover study | n=17<br>63 years | 2 nights | ? | PICO 2 | PO: sleep quality |
| Duiverman, 2008 | Netherlands | Randomised controlled study | n=72<br>62 years | 3 months | 53 | PICO 1 | PO: QOL-1<br>SO: QOL-2, 6MWT, dyspnea |
| Duiverman, 2011 | Netherlands | Randomised controlled study | n=66<br>62 years | 2 years | 50 | PICO 1 | PO: QOL-1<br>SO: QOL-2, exacerbation, hospitalisation, 6MWT, dyspnea |
| Köhnlein, 2014 | Germany<br>Austria | Multicentric prospective randomised controlled study | n=195<br>63 years | 1 year | 62 | PICO 1 | PO: mortality<br>SO: QOL, 6MWT |
| McEvoy, 2009 | Australia | Multicentric prospective randomised controlled study | n=144<br>68 years | 2 years | 65 | PICO 1 | PO: mortality<br>SO: QOL, hospitalisation |
| Meecham Jones, 1995 | United Kingdom | Randomised controlled crossover study | n=18<br>69 years | 3 months | 83 | PICO 1 | O: QOL , sleep quality, 6MWT |

**Appendix 2 – Included studies – design and patient characteristics.**

| Author, year, | Country | Study Design | No of participants (mean age, years) | Follow up period | % men | Intervention vs comparison (PICO 1 or 2) | Outcomes |
|---|---|---|---|---|---|---|---|
| Budweiser, 2007a | Germany | Prospective observational cohort | n=140<br>65 years | 20 months (13) | 65 | PICO 1 | PO: mortality |
| Clini, 1998 | Italy | Prospective observational cohort | n=49<br>66 years | 35 months (7) | 73 | PICO 1 | O: mortality, hospitalisation, ICU admissions, 6MWT, side-effects |
| Köhnlein, 2009 | Germany | Prospective observational cohort | n=80<br>57 years | 29 days (6) | 48 | PICO 1 | SO: QOL, 6MWT |
| Paone, 2014 | Italy | Prospective observational cohort | n=93<br>70 years | 2 years | 47 | PICO 1 | O: mortality, hospitalisation |
| Tsolaki, 2008 | Greece | Prospective controlled cohort | n=49<br>67 years | 1 year | 67 | PICO 1 | O: mortality, QOL, hospitalisation, exacerbation, dyspnea |

m=months, n=nights, 6MWT= 6 minute walk test, O=Any outcome when primary outcome not reported, PO=primary outcome, QOL=quality of life, SD=standard deviation, SO=secondary outcome, w=weeks.

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 3. Excluded articles

| Study author, year | Reason for exclusion |
|---|---|
| Bhatt, 2013 | Wrong population |
| Budweiser, 2007b | Wrong population |
| Budweiser, 2007c | Duplicate publication with Budweiser, 2007a |
| Budweiser, 2008 | Wrong population |
| Cano, 2014 | Wrong population |
| Casanova, 2000 | Wrong population |
| Cheung, 2011 | Wrong population |
| Clini, 1996 | Wrong population |
| Clini, 2009 | Wrong outcomes (health economy, other references) |
| De Backer, 2011 | Wrong outcomes |
| Dellweg, 2007 | Wrong outcomes |
| Diaz, 2002 | Wrong outcomes |
| Dogan, 2010 | Wrong population |
| Garrod, 2000 | Wrong population |
| Gay, 1996 | Wrong population |
| Lin, 1996 | Wrong population |
| Lukacsovits, 2012 | Wrong outcome (only measurements during ventilation) |

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 3. Excluded articles

| Study author, year | Reason for exclusion |
|---|---|
| Murphy, 2012 | Wrong intervention |
| Sin, 2007 | Wrong population |
| Struik, 2014a | Wrong population |
| Struik, 2014b | Duplicate with Struik 2013. |
| Strumpf, 1991 | Wrong population |
| Tuggey, 2003 | Wrong population (health economy, other references) |
| Windisch, 2006 | Wrong comparison |

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:1
Outcome variable: PICO 1, Mortality - Non-invasive ventilation versus standard treatment

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIV (I) | Standard care (C) | | | | |
| Clini, 2002<br>Italy | RCT | n=90<br>I=43<br>C=47 | I=8<br>C=15 | Mortality at 2 years<br>8/43 (19%) | Mortality at 2 years<br>8/47 (17%)<br>n.s. | IPAP: 14 (SD 3)<br>EPAP: 2 (SD 1)<br>BF: ?<br>Compliance: 9 (SD 2) h | + | ? | +<br>? |
| Köhnlein, 2014<br>Germany/Austria | RCT | n=195<br>I=102<br>C=93 | I=11<br>C=3 | Mortality at 1 year<br>12/102 (12%) | Mortality at 1 year<br>31/93 (33%)<br>p=0.0004 | IPAP: 21.6 (SD 4.7)<br>EPAP: 4.8 (SD 1.6)<br>BF: 16.1 (SD 3.6)<br>Compliance: 5.9 (SD 3.1) h | + | + | + |
| McEvoy, 2009<br>Australia | RCT | n=144<br>I=72<br>C=72 | I=4<br>C=4 | Mortality<br>Mean follow up 28.5m<br>40/72 (56%)<br><br>Hazard ratio (HR) adjusted:<br>0.63 (CI95%: 0.40 to 0.99)<br>p=0.045 (favours I) | Mortality<br>Mean follow up 20.5m<br>46/72 (64%) | IPAP: 13<br>EPAP: 5<br>BF: ?<br>Compliance: 4.5 (SD 3.2) h | ? | + | ? |
| Budweiser, 2007a<br>Germany | cohort | n=140<br>I=99<br>C=41 | I=12<br>C=0 | Mean follow up<br>19.8 (SD 12.9) months<br>Mortality: 24/99 (24%)<br><br>Survival rate:<br>1y: 87.7 (CI95%: 76.5 to 97.5) %<br>2y: 71.8 (CI95%: 66.6-91.0) %<br>p=0.001 | Mean follow up<br>12.9 (SD 9.9) months<br>Mortality: 18/41 (44%)<br><br>Survival rate:<br>1y: 56.7 (CI95%: 41.0 to -89.8) %<br>2y: 42.0 (CI95%: 41.4-78.9) % | IPAP: 21 (SD 4)<br>EPAP: 4.5 (SD 1.4)<br>BF: 17.3 (SD 2.5)<br>Compliance: 6.5 (SD 2.5) h | ? | + | ? |
| Paone, 2014<br>Italy | cohort | n=93<br>I=45<br>C=48 | I=0?<br>C=0? | Median follow up 24 months<br>Mortality: 13/48 (27%)<br>n.s. | Median follow up 24 months<br>Mortality: 10/45 (22%) | IPAP: 18.5 (2.7)<br>EPAP: 3.9 (1)<br>BF: ?<br>Compliance: 7.4 (1.3) h | - | ?<br>- | - |
| Tsolaki, 2008<br>Greece | cohort | n=49<br>I=27<br>C=22 | I=3<br>C=0 | Mortality<br>Mean follow up 24m<br>2/27 (8%) | Mortality<br>Mean follow up 24 m<br>2/22 (9%)<br>n.s. | IPAP: 15.3 (SD 2)<br>EPAP: 5.4 (SD 0.7)<br>BF: ?<br>Compliance: 9 (2.2) h | +<br>? | ? | ? |

EPAP = expiratory positive airway pressure in cmH2O, IPAP = inspiratory positive airway pressure in cmH2O, ITT = intention to treat, NIV = non-invasive ventilation.
RCT = randomised controlled trial.

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:2
Outcome variable: PICO 1, Health related quality of life (HRQL)

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIV (I) | Standard care (C) | | | | |
| Clini, 2002<br>Italy | RCT | I=43<br>C=47 | I=8<br>C=15 | At 2 years<br>SGRQ: -5%, n.s.<br><br>Significant improvement in MRF-28 compared with C.<br>p=0.041 | At 2 years<br>SGRQ: -4%<br><br>Numbers not reported | SGRQ<br><br>MRF-28 | + | ? | +<br>? |
| Duiverman, 2008<br>Netherlands | RCT | I=37<br>C=35 | I=13<br>C=3 | <u>CRQ total points</u><br>Baseline: 81.7 (SD 16)<br>At 3 months: 96.8 (SD 15)<br>Intergroup difference in change: 7.5 (CI95%: -1.0 to 16)<br>n.s.<br><br><u>CRQ domain fatigue</u><br>Baseline: 13.8 (SD 4)<br>At 3 months: 18.8 (SD 4)<br>Intergroup difference in change: 3.3 (CI95%: 0.8 to 5.7)<br>Sign. (p-value not reported, (favours I)<br><br>CRQ domains dyspnea, emotion, and mastery: n.s.<br><br><u>MRF-28 total:</u><br>Baseline: 55.3 (SD 24)<br>At 3 months: 44.6 (SD 22)<br>Intergroup difference in change: -9.7 (CI95%: -18 to -1)<br>Sign. (p-value not reported, (favours I) | <u>CRQ total points</u><br>Baseline: 79.3 (SD 19)<br>At 3 months: 87.9 (SD 20)<br><br><u>CRQ domain fatigue</u><br>Baseline: 13.6 (SD 5)<br>At 3 months: 15.4 (SD 6)<br><br><u>MRF-28 total:</u><br>Baseline: 52.2 (SD 24)<br>At 3 months: 52.1 (SD 24) | CRQ, MRF-28, SRI | + | + | + |

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:2
Outcome variable: PICO 1, Health related quality of life (HRQL)

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIV (I) | Standard care (C) | | | | |
| (Duiverman, 2008 cont'd) | | | | <u>MRF-28 cognition subscale</u><br>Baseline: 50.0 (SD 33)<br>At 3 months: 28.3 (SD 25)<br>Intergroup difference in change: -22 (CI95%: -35 to -9)<br>Sign. (p-value not reported, (favours I))<br><br>MRF-28 <u>cognition subscale</u> domains daily activities, invalidity: n.s.<br><br>SRI total, and all domains: n.s<br>HADS: n.s. | <u>MRF-28 cognition subscale</u><br>Baseline: 35.2 (SD 39)<br>At 3 months: 40.6 (SD 38) | HADS data not reported | | | |

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:2
Outcome variable: PICO 1, Health related quality of life (HRQL)

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIV (I) | Standard care (C) | | | | |
| Duiverman, 2011<br>Netherlands | RCT | I=37<br>C=35 | I=16<br>C=15 | <u>CRQ total points</u><br>Change up to 24 months:<br>-3.6 (CI95%: -10.1 to 2.9)<br>n.s<br>CRQ domain scores: n.s.<br><br><u>MRF-28 total score</u><br>Change up to 24 months:<br>3.8 (CI95% -3.4 to 11.1)<br>Intergroup difference in change:<br>-13.4 (CI95%: -22.7 to -4.2)<br>p=0.005 (favours I)<br><br><u>MRF 28 daily activities subscale</u><br>Change up to 24 months:<br>1.9 (CI95%: -8.0 to 11.8)<br>Intergroup difference in change:<br>-18.1 (CI 95%: -31.0 to -5.3)<br>p<0.05 (favours I)<br><u>MRF 28 daily invalidity subscale</u><br>Change up to 24 months:<br>0.6 (CI95%: -9.7 to 10.9)<br>Intergroup difference in change:<br>-15.5 (CI 95%: -29.0 to -2.3)<br>p<0.05 (favours I)<br><br>MRF 28 cognition subscale: n.s<br><br><u>SRI</u><br>Change up 24 months<br>-3.4 (CI95%: -7.1 to 0.4)<br>Intergroup difference in change *:<br>2.9 (CI95%: -1.9 to 7.8)<br>n.s. | <u>CRQ total points</u><br>Change up to 24 months:<br>-2.3 (CI95%: -7.8 to 3.2)<br><br><u>MRF-28 total score</u><br>Change up to 24 months:<br>17.2 (CI95%: 11.6 to 23.1)<br><br><u>MRF 28 daily activities subscale</u><br>Change up to 24 months:<br>20.2 (CI95% 11.8 to 28.1)<br><br><u>MRF 28 daily invalidity subscale</u><br>Change up to 24 months:<br>16.2 (CI95%: 7.6 to 24.8)<br><br><u>SRI</u><br>Change up 24 months<br>-6.3 (CI95%: -9.2 to -3.2) | CRQ, MRF-28, SRI, HADS<br><br>For MRF 28: a negative number indicates more improvement over time | + | ? | +<br>? |

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:2
Outcome variable: PICO 1, Health related quality of life (HRQL)

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIV (I) | Standard care (C) | | | | |
| (Duiverman, 2011, cont'd) | | | | <u>SRI Physical Functioning</u><br>Change up 24 months<br>-0.8 (CI95%: -6.3 to 4.4)<br>Intergroup difference in change [*]:<br>Δ -10.7% (CI95% -3.8 to -17.6)<br>p=0.003 (favours I)<br><br>SRI domains, respiratory complaints, attendant symptoms and sleep, social relationships, anxiety, psychological well-being, social functioning: n.s<br><br><u>HADS total points</u><br>Change up 24 months<br>-0.2 (CI95%: -3.4 to 2.7)<br>Intergroup difference in change:<br>-4.0 (CI95%: -7.8 to 0.0)<br>p<0.05 (favours I) | <u>SRI Physical Functioning</u><br>Change up 24 months<br>-11.6 (CI95%: -16.0 to - )[†]<br><br><u>HADS total points</u><br>Change up 24 months<br>3.6 (CI95%: 1.3 to 5.9) | [*]Adjusted for baseline values<br><br>[†] missing data for the second CI95% value in article supplement | | | |

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:2
Outcome variable: PICO 1, Health related quality of life (HRQL)

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIV (I) | Standard care (C) | | | | |
| Köhnlein, 2014<br>Germany, Austria | RCT | I=102<br>C=93 | I=11<br>C=3 | <u>SF-36</u><br>Intergroup difference: n.s<br><br><u>SF-36 General health perception subscale:</u><br>Δ 8.6 (CI95% 1.8-13.3)<br>p=0.0013 (favours I)<br><br>SF-36 subscales physical functioning, role physical, bodily pain, vitality, social functioning, role emotional, mental health, physical component, mental component: n.s.<br><br><u>SGRQ summary score</u><br>Δ 6.2 (CI95% 0.7-11.8)<br>p=0.0289 (favours I)<br><br>SRI improved compared with C.<br>Δ 5.6 (CI95% 0.1-11.1)<br>p=0.0445 (favours I) | Numbers not given | SGRQ, SF-36, SRI | + | + | + |

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:2
Outcome variable: PICO 1, Health related quality of life (HRQL)

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIV (I) | Standard care (C) | | | | |
| McEvoy, 2009<br>Australia | RCT | I=72<br>C=72 | I=4<br>C=4 | <u>SF-36 General health subscale at 12 months</u>:<br>Median: 20.0 (IQR 26.3)<br>p=0.002 (favours C)<br><br><u>SF-36 Mental health subscale at 12 months</u>:<br>Median: 70.0 (IQR 40.0)<br>p=0.009 (favours C)<br><br>SF-36 subscales physical functioning, role physical, bodily pain, vitality, social functioning, role emotional: n.s.<br><br>SGRQ at 12 months: n.s<br><br><u>POMS Confusion/bewilderment subscale at 12 months:</u><br>Median: 5.0 (IQR 6.3)<br>p=0.020 (favours C)<br><br><u>POMS Vigour subscale at 12 months:</u><br>Median: 11.0 (IQR 6.5)<br>p=0.05 (favours C)<br><br>POMS subscales, depression-dejection, anger-hostility, fatigue, tension-anxiety, total mood: n.s. | <u>SF-36 General health subscale at 12 months</u>:<br>Median: 32.0 (IQR 25.0)<br><br><u>SF-36 Mental health subscale at 12 months</u>:<br>Median: 80.0 (IQR 16.0)<br><br><u>POMS Confusion/bewilderment subscale at 12 months:</u><br>Median: 3.0 (IQR 4.0)<br><br><u>POMS Vigour subscale at 12 months:</u><br>Median: 14.0 (IQR 10.5) | SGRQ, SF-36, POMS | ? | ?<br>- | ? |

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:2
Outcome variable: PICO 1, Health related quality of life (HRQL)

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIV (I) | Standard care (C) | | | | |
| Meecham Jones, 1995 UK | RCT | 18 Cross-over design | 4 | <u>SGQR total score at 3 months</u> p=0.03 (favours I)<br><br><u>SGQR impacts score at 3 months</u> p=0.002 (favours I)<br><br><u>SGQR symptom score at 3 months</u> p=0.03 (favours I)<br><br><u>SGQR activity score at 3 months</u> n.s. | Numbers not reported | SGRQ | ? - | ? - | ? |
| Tsolaki, 2008 Greece | Cohort | I=27 C=22 | I=3 C=0 | SF-36 subscores Physical and Mental components both p<0.001 (favours I) | Numbers not reported | SF-36 numbers not given (graph) | + ? | ? | ? |

CRQ = chronic respiratory questionnaire, HADS = hospital anxiety and depression scale, MRF-28 = Maugeri foundation respiratory failure questionnaire, NIV = non-invasive ventilation, POMS = profile of mood states, RCT = randomised controlled trial, SRI = severe respiratory insuffiency questionnaire (with a range of 0-100 units, where high values indicate high HRQL and converse), SF-36 = short form-36, SGRQ = st Georges respiratory questionnaire (scores range from 0 to 100, with higher scores indicating more limitations).

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:3
Outcome variable: PICO 1, Sleep Efficiency

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIV (I) | Standard care (C) | | | | |
| Clini, 2002<br>Italy | RCT | I=43<br>C=47 | I=8<br>C=15 | Sleep score<br>Baseline: 2.5 (SD 1.1)<br>2 years: 1.7 (SD 0.8)<br>n.s | Sleep score<br>Baseline: 2.2 (SD 1.2)<br>2 years: 2.3 (SD 1.3) | Semi qualitative multipoint scale ranging from 1 (best) to 4 (worst) | + | - | + ? |
| Meecham Jones, 1995<br>United Kingdom | RCT | 18<br>Cross-over design | 4 | <u>Sleep efficiency</u><br>Baseline: 51 (33-73) %<br>At 3 months: 81 (66-88) %<br>Intergroup difference:<br>8 (CI95%: 3 to 18) %<br>p=0.05 (favours I)<br><br><u>Total sleep time at 3 months</u><br>Intergroup difference:<br>56 (CI95%: 37 to 107) min<br>p<0.001 (favours I) | Not reported | PSG, Total sleep time, Sleep efficiency | ? - | ? - | ? |

NIV = non-invasive ventilation, PSG = polysomnography, RCT = randomised controlled trial.

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:4
Outcome variable: PICO 1, Hospitalisation

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIV (I) | Standard care (C) | | | | |
| Clini, 2002<br>Italy | RCT | I=43<br>C=47 | I=8<br>C=15 | Hospital admissions during 2 years: 0.9 (SD1.2)<br>n.s | Hospital admissions during 2 years: 1.4 (SD 2.3) | | + | - | +<br>? |
| Duiverman, 2011<br>Netherlands | RCT | I=37<br>C=35 | I=16<br>C=15 | Intergroup difference: n.s | Not reported | The median hospitalisation rate varied between 0-2 hospitalisations per year | + | - | +<br>? |
| McEvoy, 2009<br>Australia | RCT | I=72<br>C=72 | I=4<br>C=4 | Hospitalisation rate during 2 years:<br>0.032<br>n.s | Hospitalisation rate during 2 years:<br>0.031 | | ? | - | ? |
| Clini, 1998<br>Italy | cohort | I=28<br>C=21 | ? | n.s.<br>. | Not reported | Hospital stay. Less ICU admissions | ? | ?<br>- | - |
| Paone, 2014<br>Italy | cohort | I=48<br>C=45 | I=0?<br>C=0? | Hospitalisations during 24 months<br>Median:1 (IQR 0-2)<br>p=0.01 | Hospitalisations during 24 months<br>Median: 2 (IQR 1-4) | Hospitalisation rate | - | ?<br>- | ?<br>- |
| Tsolaki, 2008<br>Greece | cohort | I=27<br>C=22 | I=3<br>C=0 | Days in hospital<br>6.6 (SD 14.1)<br>Δ -9.4 days/year<br>p=0.023 | Days in hospital<br>16.0 (SD 12.9) | Hospitalisation rate not reported | ? | ?<br>- | ? |

NIV = non-invasive ventilation, RCT = randomised controlled trial.

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:5
Outcome variable: PICO 1, Exacerbations

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIV (I) | Standard care (C) | | | | |
| Duiverman, 2011 Netherlands | RCT | I=37 C=35 | I=16 C=15 | Median exacerbation frequency: 3.0 per year n.s. | Median exacerbation frequency: 3.0 per year | | + | ? | + ? |
| Tsolaki, 2008 Greece | Cohort | I=27 C=22 | I=3 C=0 | Mean number of exacerbations: 1.4 (SD 2.1) n.s | Mean number of exacerbations: 1.8 (SD 1.4) | | + ? | ? | ? |

RCT = randomised controlled trial.

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:6
Outcome variable: PICO 1, Six-minute walk test (6MWT)

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIV (I) | Standard care (C) | | | | |
| Clini, 2002<br>Italy | RCT | I=43<br>C=47 | I=8<br>C=15 | Baseline:<br>201 (SD 125) m<br><br>Intergroup difference at 12 months:<br>Δ 4.4 (CI95%: -37.5 to 28.6) m<br>n.s.<br><br>Intergroup difference at 24 months:<br>Δ 3.3 (CI95%: -39.0 to 45.7) m<br>n.s. | Baseline:<br>247 (SD 110) m | | + | ? | +<br>? |
| Diaz, 2005<br>Chile | RCT | I=27<br>C=15 | I=0<br>C=0 | Baseline:<br>329 (SD 103) m<br><br>At 5 weeks<br><u>Intergroup difference:</u><br>Δ 63 m<br>p<0.001<br><br>70% of the intervention group participants reached MID | Baseline:<br>380 (SD 94) m<br><br>None of the control group participants reached MID | The control intervention was sham-NIV<br><br>6MWT<br>MID (minimal important difference), in this study defined as 54 m | + | ? | ? |
| Duiverman, 2008<br>Netherlands | RCT | I=37<br>C=35 | I=13<br>C=3 | Baseline: 318 (SD 131) m<br>At 3 months:<br>340 (SD 119) m<br>Intergroup difference in Δ:<br>2 (CI95%: -19 to 23) m<br>n.s. | Baseline: 304 (SD 112) m<br>At 3 months:<br>325 (SD 108) m | Other related findings:<br>Daily step count significantly improved | + | + | + |
| Duiverman, 2011<br>Netherlands | RCT | I=35<br>C=37 | I=16<br>C=15 | Change up to 24 months:<br>-4 (CI95%: -28 to 19) m<br>Intergroup difference in Δ:<br>77.3 (CI95%: 46.4 to 108.0) m<br>p<0.001 | Change up to 24 months:<br>-82 (CI95%: -103 to 62) m | | + | ? | +<br>? |

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:6
Outcome variable: PICO 1, Six-minute walk test (6MWT)

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIV (I) | Standard care (C) | | | | |
| Köhnlein, 2014<br>Germany, Austria | RCT | I=102<br>C=93 | I=11<br>C=3 | At 12 months:<br>Δ: 0.0 (CI95%: -5.5 to 5.8) %<br>Intergroup difference:<br>Δ 7.6 (CI95%: -0.5 to 16.2) m<br>n.s. | At 12 months:<br>Δ: 7.6 (CI95%: -0.5 to 16.2) % | | + | + ? | + |
| Meecham Jones, 1995<br>United Kingdom | RCT | 18<br>Crossover design | 4 | Baseline:<br>Median: 250 (range 100-425) m<br>At 12 months:<br>Median: 240 (range 100-450) m<br>n.s. | Baseline:<br>Median: 250 (range 100-425) m<br>At 12 months:<br>Median: 235 (range 80-440) m | | ? - | ? - | ? |
| Clini, 1998<br>Italy | cohort | I=28<br>C=21 | ? | Baseline: 245 (SD 78) m<br><br>At 12 months:<br>250 (SD 88) m, n.s.<br><br>At 24 months:<br>291 (SD 75) m<br>Intergroup difference:<br>Δ > 50m, p<0.01<br><br>At 36 months:<br>284 (SD 89) m, p<0.01<br><br>Intergroup difference:<br>Δ > 75 m, p<0.01 | Data not reported | Intergroup difference at 36 months estimated from graph | ? | ? - | - |
| Köhnlein, 2009<br>Germany | cohort | I=43<br>C=40 | I=3<br>C=0 | Baseline:<br>243 (SD 91) m<br><br>At 12 months:<br>325 (CI95%: 60.6 to 101.8 ) m<br>p=0.04 | Baseline:<br>245 (SD 88) m<br><br>At 12 months:<br>295 (CI 95%: 35.6 to 63.1) m | MID in this patient group was 35 m | + | ? | ? |

6MWT = six-minute walk test, MID = minimal important difference, RCT = randomised controlled trial.

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:7
Outcome variable: PICO 1, Dyspnoea

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIV (I) | Standard care (C) | | | | |
| Clini, 2002<br>Italy | RCT | I=43<br>C=47 | I=8<br>C=15 | Significantly improved compared with C at 2 years<br><br><u>Intergroup difference:</u><br>Δ: 0.60 (CI 95%: 0.15 to 1.05)<br>p=0.013 (favours NIV) | Not reported | MRC-score | + | ? | +<br>? |
| Diaz, 2005<br>Chile | RCT | I=27<br>C=15 | I=0<br>C=0 | TDI at 5 weeks:<br>Δ 3.1 (SD 1.2) units<br>p<0.0001<br><br>Baseline (Borg):<br>6.6 (SD 1.7)<br>At 5 weeks (Borg)<br>5.1 (SD 1.7)<br><u>Intergroup difference:</u><br>Δ: 1.4<br>p<0.0001 intergroup | TDI at 5 weeks:<br>Δ 0.07 (SD 0.7)<br><br>Baseline (Borg):<br>6.3 (SD 1.8)<br>At 5 weeks (Borg)<br>6.2 (SD 1.4) | The control intervention was sham-NIV<br>TDI (Transition Dyspnea Index). Minimal clinical important difference: one unit<br>Borg scale points after six minute walk test | + | ? | ? |
| Duiverman, 2008<br>Netherlands | RCT | I=37<br>C=35 | I=13<br>C=3 | At 3 months: n.s. | Not reported | Data not reported. MRC-score | + | + | + |
| Duiverman, 2011<br>Netherlands | RCT | I=37<br>C=35 | I=16<br>C=16 | <u>MRC change up to 24 months</u><br>0.2 (CI95%: -0.2 to 0.4)<br><u>Intergroup difference in Δ</u>:<br>-0.4 (CI95%: -0.8 to 0.0)<br>p=0.05 (favours I) | <u>MRC change up to 24 months</u><br>0.6 (CI95%: 0.4 to 0.8) | MRC-score | + | ? | +<br>? |

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:7
Outcome variable: PICO 1, Dyspnoea

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIV (I) | Standard care (C) | | | | |
| Clini, 1998<br>Italy | cohort | I=28<br>C=21 | ? | At 3 years:<br>n.s. | Not reported | Data not reported. ATS-score | ? | ?<br>- | - |
| Tsolaki, 2008<br>Greece | cohort | I=27<br>C=22 | I=3<br>C=0 | At 1 year<br><u>Intergroup difference:</u><br>Δ approx. -1.2 units<br>p=0.001 | Not reported | MRC-score, Numbers not given. Intergroup difference estimated from graph. | +<br>? | ? | ? |

ATS = American thoracic society dyspnoea score, MRC = medical research council score (minimal clinical important difference for MRC-score: 0.4; range = 0-5 units, where higher score implicates more dyspnoea), NIV = non-invasive ventilation, RCT = randomised controlled trial, TDI = transition dyspnoea index, which ranges from - 9 to + 9. Higher score indicates more improvement of dyspnoea (Minimal important difference: change of ≥1 unit), Borg scale ranges from 6 to 20 units, where higher scores reflect maximal dyspnoea at exertion (Minimal important difference: change of ≥1 unit).

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:8
Outcome variable: PICO2, HRQoL

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | High NIV (I) | Low NIV (C2) | | | | |
| Dreher, 2010 Germany | RCT | 17 cross-over | 4 | At 6 weeks <u>Intergroup difference</u> Δ -0.14 (95%CI: -4.9 to 4.6) n.s. | Not reported | SRI | ? - | - | + |

NIV = non-invasive ventilation, RCT = randomised controlled trial, SRI = severe respiratory insufficiency questionnaire summary (score with a range of 0-100, where high values indicate high HRQL and converse).

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:9
Outcome variable: PICO2, Sleep efficiency, PICO2

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | High NIV (I) | Low NIV (C2) | | | | |
| Dreher, 2011 Germany | RCT | 17 cross-over | 4 | After two nights: Intergroup difference Δ 4 (CI95%: -3.6 to 11.6) % Improved sleep efficiency n.s. | | Measured by polysomnography | ? - | - | + |

NIV = non-invasive ventilation, RCT = randomised controlled trial.

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:10
Outcome variable: PICO2, Six-minute walk test (6MWT)

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | High NIV (I) | Low NIV (C2) | | | | |
| Dreher, 2010<br>Germany | RCT | 17<br>cross-over | 4 | At 6 weeks<br><u>Intergroup difference</u><br>6MWT:<br>Δ 14 (-42 to 70) m<br>n.s. | Not reported | | ?<br>- | - | + |

6MWT = six-minute walk test (Minimal clinical important difference = 35 m), NIV = non-invasive ventilation, RCT = randomised controlled trial.

Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:11
Outcome variable: PICO 2: Dyspnoea

* + No or minor problems
? Some problems
- Major problems

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts | Results | | Comments | * Directness | * Study limitations | * Precision |
|---|---|---|---|---|---|---|---|---|---|
| | | | | High NIV (I) | Low NIV (C2) | | | | |
| Dreher, 2010 Germany | RCT | 17 cross-over | 4 | At 6 weeks <u>Intergroup difference</u> Δ -2.4 (95%CI: -4.3 to -0.4) p=0.025 | Not reported | Borg Dyspnea Scale. Minimal clinical important difference: 1 unit. After 6MWT. | ? - | - | + |

NIV = non-invasive ventilation, RCT = randomised controlled trial.

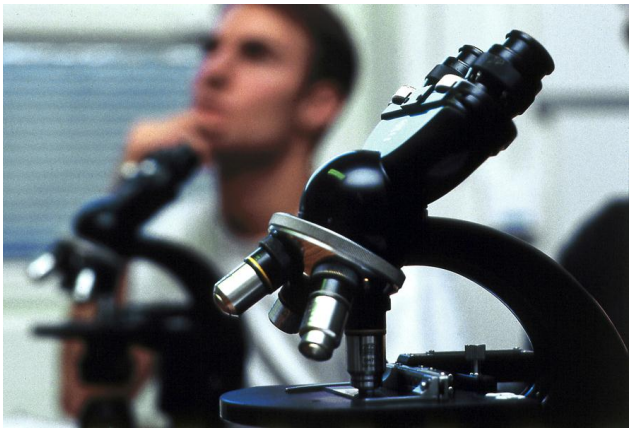
Project: Home mechanical ventilation in chronic hypercapnic COPD patients
Appendix 4:12
Outcome variable: Complications

| Author, year, country | Study design | Number of patients n= | With drawals - dropouts (incl death) | Results | | Comments |
|---|---|---|---|---|---|---|
| | | | | NIV (I) | Standard care (C) | |
| Köhnlein, 2014<br>Germany, Austria | RCT | I=102<br>C=93 | I=11<br>C=3 | 14% Facial skin rash | NA | No severe adverse events |
| Clini, 1998<br>Italy | cohort | I=28<br>C=21 | ? | 21% Nasal skin lesions<br>14% Gastric distension<br>14% Rhinorrhoea<br>7 % Mucosal dryness<br>4 % Skin inflammation | NA | No severe adverse events |

NIV = non-invasive ventilation, RCT = randomised controlled trial, NA = not applicable.

# Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



## HTA

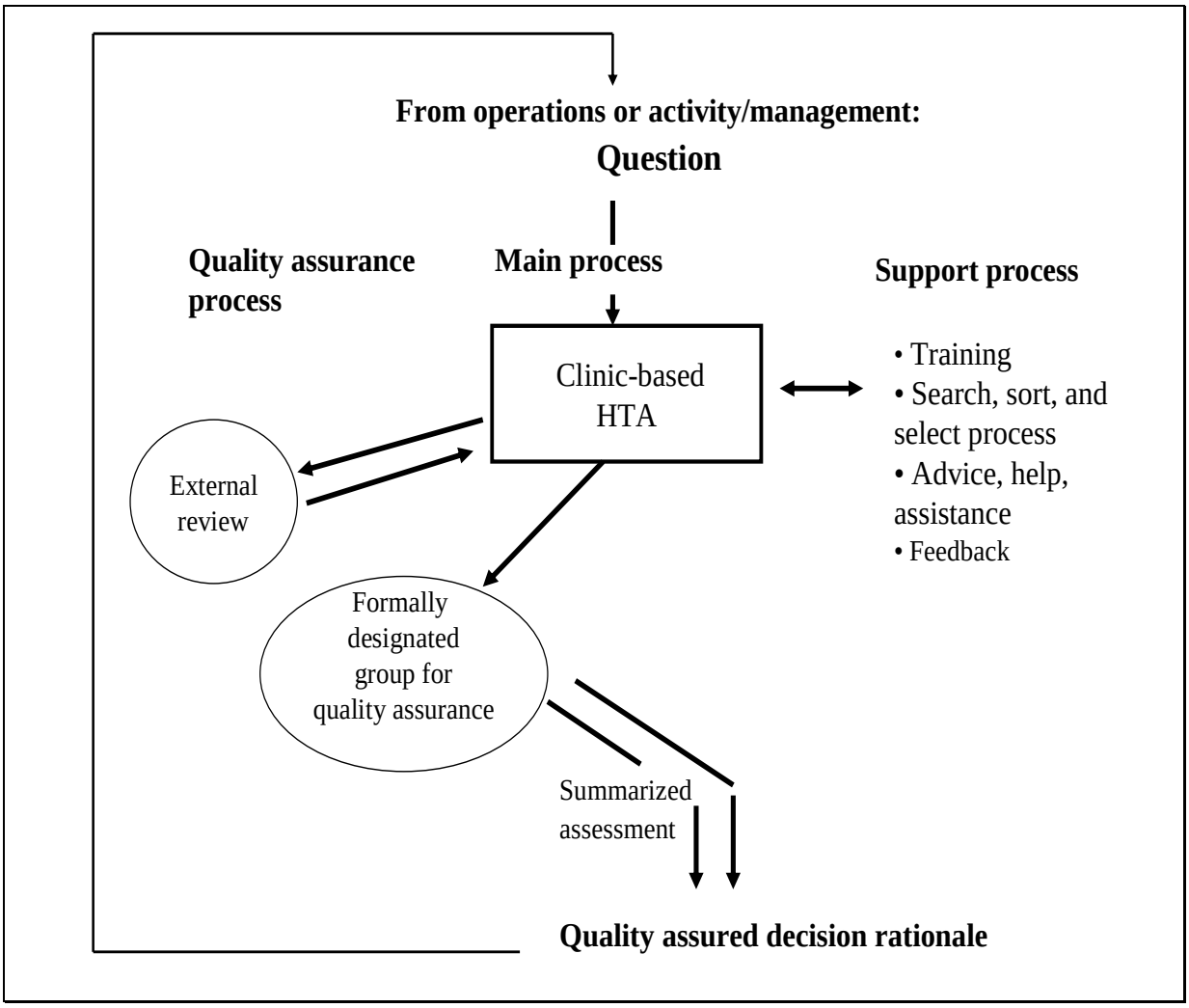
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

| | |
|---|---|
| High quality of evidence | = (GRADE⊕⊕⊕⊕ ) |
| Moderate quality of evidence | = (GRADE ⊕⊕⊕O) |
| Low quality of evidence | = (GRADE ⊕⊕OO) |
| Very low quality of evidence | = (GRADE ⊕OOO) |

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Sahlgrenska Universitetssjukhuset, HTA-centrum
Röda Stråket 8, 413 45 Göteborg
www.sahlgrenska.se/hta-centrum