Technology Assessment Program
Number xx

Home Mechanical Ventilators

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Agency for Healthcare Research and Quality
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Key Messages

Purpose of review
To evaluate home noninvasive positive pressure ventilation (NIPPV) in adults with chronic respiratory failure in terms of initiation, continuation, effectiveness, adverse events, equipment parameters and required respiratory services. Devices evaluated were home mechanical ventilators (HMV), bi-level positive airway pressure (BPAP) devices, and continuous positive airway pressure (CPAP) devices.

Key messages
- In COPD, home BPAP (compared to no device) was associated with lower mortality, intubations, hospital admissions, and no change in quality of life (low to moderate SOE). HMV (compared individually with BPAP, CPAP, or no device) was associated with fewer hospital admissions (low SOE). In thoracic restrictive diseases, home HMV (compared to no device) was associated with lower mortality (low SOE). In neuromuscular diseases, home BPAP (compared to no device) was associated with lower mortality and better quality of life (low SOE).
- Current comparative evidence is not available to assess the impact of many NIPPV device capabilities on patient outcomes; particularly comparing HMV to BPAP. Future comparative studies should address which device capabilities are associated with improved patient outcomes.
- Criteria to initiate home NIPPV and home respiratory services were summarized in this report but varied and were not validated in comparative studies.
- Incidence of non-serious adverse events such as facial rash, dry eyes, mucosal dryness, mask discomfort was around 0.3 across devices. The most commonly reported serious adverse event was acute respiratory failure. Based on direct comparisons, we found no statistically significant differences in number of treatment withdrawals or adverse events when comparing different devices or when comparing device use with no device use.
This report is based on research conducted by an Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. xxx-xxxx-xxxxxx). The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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The Centers for Medicare & Medicaid Services requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the following EPC (to be inserted in final report) (Contract Number: xxx-xxxx-xxxxx).

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new health care technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

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In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who provided input to this report follows: To be provided in the Final Report.
Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

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The list of Peer Reviewers follows: To be provided in the Final Report
Structured Abstract

Objectives. To evaluate home noninvasive positive pressure ventilation (NIPPV) in adult patients with chronic respiratory failure in terms of initiation, continuation, effectiveness, adverse events, equipment parameters and required respiratory services. We evaluated respiratory failure primarily due to chronic obstructive pulmonary disease (COPD), thoracic restrictive disorders, and neuromuscular disease.

Data sources. National Guideline Clearinghouse, MEDLINE, EMBASE, SCOPUS, Cochrane Central Registrar of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus from January 1, 1995 to June 26, 2018.

Review methods. We included randomized and comparative observational studies that enrolled adults with chronic respiratory failure who used NIPPV for ≥ 1 month at home (using a home mechanical ventilator [HMV], bi-level positive airway pressure [BPAP] device, or continuous positive airway pressure [CPAP] device).

Results. We included 61 studies evaluating 53,414 patients. In COPD (34 studies), common criteria for NIPPV initiation were FEV1<50% normal, PaCO2 >45mmHg, pH>7.35, and/or hypoxia. BPAP (compared with no device) was associated with reductions in mortality (moderate Strength of Evidence [SOE]), need for intubation (moderate SOE), and hospital admissions (low SOE). HMV (compared individually to BPAP, CPAP, or no device) was associated with fewer hospital admissions (low SOE). In patients with thoracic restrictive diseases (7 studies), common criteria for NIPPV initiation were PaCO2>45mmHg, and FVC<40% normal or MIP<60cmH2O, or nocturnal SaO2<88% for ≥ 5 consecutive minutes. HMV (compared with no device) was associated with lower mortality (low SOE). In patients with neuromuscular disease (13 studies), common criteria for NIPPV initiation were PaCO2>45mmHg or FVC<50% or MIP <60cmH2O, or nocturnal SaO2 < 88% for ≥ 5 consecutive minutes. BPAP (compared with no device) was associated with reduced mortality (low SOE), and better quality of life (low SOE). Evidence was insufficient to compare initiation criteria or determine the effect of specific home respiratory services on outcomes.

Approximately one third of patients who use NIPPV via any device experienced non-serious adverse events such as facial rash, mucosal dryness, mask discomfort, etc. Based on direct comparisons, we found no significant differences in adverse events between devices or between devices and no device.

Conclusions. In COPD, home BPAP (compared to no device) was associated with lower mortality, intubations, hospital admissions, and no change in quality of life. HMV (compared individually with BPAP, CPAP, or no device) was associated with fewer hospital admissions. In thoracic restrictive diseases, home HMV (compared to no device) was associated with lower mortality. In neuromuscular diseases, home BPAP (compared to no device) was associated with lower mortality and better quality of life. Current comparative evidence is not available to assess the impact of many device capabilities on patient outcomes. Criteria to initiate home NIPPV and home respiratory services vary and are not validated in comparative studies.
# Contents

Key Messages ................................................................................................................................... ii  
Purpose of review ............................................................................................................................ ii  
Key messages ................................................................................................................................. ii  
Structured Abstract ........................................................................................................................ vii  
Evidence Summary ....................................................................................................................... ES-1  
Introduction ..................................................................................................................................... 1  
  
  Background ...................................................................................................................................... 1  
  
  Scope and Key Questions ........................................................................................................... 1  
  Scope of the Review .................................................................................................................... 1  
  
  Key Questions .......................................................................................................................... 2  
  
  Organization of the Report ....................................................................................................... 4  
The Methods ...................................................................................................................................... 5  
  
  Literature Search Strategy ........................................................................................................... 6  
    Search Strategy ........................................................................................................................ 6  
    
    Inclusion and Exclusion Criteria ............................................................................................. 6  
    
    Study Selection ....................................................................................................................... 6  
    
    Data Extraction ....................................................................................................................... 6  
    
    Assessment of Risk of Bias of Individual Studies .................................................................. 7  
    
    Data Synthesis ......................................................................................................................... 7  
    
    Grading the Strength of Evidence ........................................................................................... 8  
    
    Assessing Applicability .......................................................................................................... 9  
    
    Peer Review and Public Commentary .................................................................................... 9  

The Results ..................................................................................................................................... 10  
  
  Literature Searches and Evidence Base .................................................................................... 10  
  
  Chronic Obstructive Pulmonary Disease (COPD) ................................................................. 11  
    Key Points-KQ1 ..................................................................................................................... 11  
    Key Points-KQ2 ..................................................................................................................... 13  
    Key Points-KQ3 ..................................................................................................................... 19  
    Key Points-KQ4 ..................................................................................................................... 20  
  
  Thoracic Restrictive Diseases ....................................................................................................... 22  
    Key Points-KQ1 ..................................................................................................................... 22  
    Key Points-KQ2 ..................................................................................................................... 23  
    Key Points-KQ3 ..................................................................................................................... 25  
    Key Points-KQ4 ..................................................................................................................... 26  
  
  Neuromuscular Disease (NMD) ................................................................................................. 26  
    Key Points-KQ1 ..................................................................................................................... 26  
    Key Points-KQ2 ..................................................................................................................... 27
Table 10. Other effectiveness outcomes (HMV vs. no device in patients with thoracic restrictive
diseases) .........................................................................................................................................24
Table 11. Major effectiveness outcomes with SOE (all devices in patients with neuromuscular
disease) ...........................................................................................................................................29
Table 12: Other effectiveness outcomes (all devices in patients with neuromuscular disease) ....29
Table 13: Major effectiveness outcomes with SOE (all devices in patients with obesity
hypoventilation syndrome) ............................................................................................................35
Table 14. Other effectiveness outcomes (all devices in patients with obesity hypoventilation
syndrome) ......................................................................................................................................36
Table 15. Effectiveness of HMV vs. no device in patients with other respiratory diseases .......40
Table 16. Major effectiveness outcomes with SOE (all devices in studies with mixed disease
conditions) ......................................................................................................................................44
Table 17. Other effectiveness outcomes (all devices in studies with mixed disease conditions)..44
Table 18. Incidence rate of adverse events by device .................................................................47
Table 19. Types of reported serious adverse events .................................................................48
Table 20. Comparisons of total number of adverse events and by devices and diseases ........48
Table 21. Summary of device effectiveness in patients with COPD .............................................50
Table 22. Summary of device effectiveness in patients with thoracic restrictive diseases........51
Table 23. Summary of device effectiveness in patients with neuromuscular disease ..............52
Table 24. Summary of device effectiveness in patients with obesity hypoventilation syndrome .52
Table 25. Summary of device effectiveness in patients with other respiratory diseases ..........52
Table 26. Summary of device effectiveness in patients with mixed respiratory diseases ........52

**Figures**

Figure 1. Analytic framework ......................................................................................................5
Figure 2. Studies by disease, device, and study design ..............................................................10
Figure 3. Evidence map for effectiveness of device use ............................................................50

**Appendixes**

Appendix A. Flow Chart
Appendix B. Search Strategy
Appendix C. Excluded Studies
Appendix D. Characteristics of Included Studies
Appendix E. Risk of Bias
Appendix F. Results from the Included Studies
Appendix G. Guidelines
Appendix H. Figures
Appendix I. References for Appendixes
Evidence Summary

Background and Objectives

Chronic respiratory failure is a common medical condition characterized by the inability to maintain normal oxygen (PaO$_2$ $\geq$ 60mmHg) and/or carbon dioxide (PaCO$_2$ $\leq$ 45mmHg) levels. Many diseases may lead to chronic respiratory failure including chronic obstructive pulmonary disease (COPD), thoracic restrictive diseases (TRD) such as kyphoscoliosis, neuromuscular diseases (NMD), and obesity hypoventilation. Associated with increased morbidity and mortality, chronic respiratory failure may range from mild to severe and may be stable or progressive.

Chronic respiratory failure is treated with chronic mechanical ventilation. Mechanical ventilator devices are broadly classified into two categories: home mechanical ventilators (HMV) and bi-level positive airway pressure (BPAP) devices. While both HMV and BPAP devices provide positive pressure ventilation, their technical features may vary considerably. Variability includes: interface (tracheostomy or mask), mode of ventilation (such as pressure targeted versus volume targeted), respiratory circuit (such as single-limb versus double-limb), monitoring capability, safety and alarm systems, and internal battery life. Devices also differ by level of oversight and servicing.

If deemed to be feasible and safe, using these devices in the home setting is preferred to other settings such as intensive care units (ICUs), ventilator weaning units, or long-term care hospitals. Advantages of home use include lower costs, greater independence, increased quality of life, decreased risk of hospital-acquired infections, and reduced use of acute care facilities. The number of patients using long-term HMVs and BPAP devices is growing.

For patients who use home mechanical ventilation through a noninvasive interface, or noninvasive positive pressure ventilation (NIPPV), selecting the optimal device type (HMV versus BPAP versus continuous positive airway pressure [CPAP]) and device settings is imperative. Depending on the severity of illness, patients with chronic hypercapnic respiratory failure may require no, intermittent, or continuous ventilatory support. Failing to adequately treat chronic respiratory failure with the appropriate device could potentially result in sudden or gradual hypoxemia and/or hypercapnia. This can lead to poor quality of life, sleepiness, hospital admission, intubation, and even respiratory arrest and death.

Currently, substantial variability exists regarding the usage, prescribing patterns, policies, and guidelines among noninvasive HMVs, BPAPs, and CPAPs. While a number of guidelines address home use of BPAPs and HMVs, there is marked variability in the conclusions, recommendations, and evidence basis for these guidelines. With current practice and guideline variability, there is a clear need to synthesize the best available evidence to guide prescribing.

This systematic review evaluates home NIPPV in adult patients with chronic respiratory failure primarily due to chronic obstructive pulmonary disease (COPD), thoracic restrictive disorders, and neuromuscular disease. Other causes of respiratory failure were included due to additional interest.
Scope and Key Questions

Scope of Review

This systematic review addresses initiation and continuation of home NIPPV including the effectiveness, equipment settings, and related respiratory services for patients with chronic respiratory failure. The systematic review also highlights areas of controversy and identifies needs for future research. NIPPV in other settings were excluded (e.g. long term acute care hospital, skilled nursing facility, etc.)

Key Questions

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bilevel Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface for the population of patients with chronic respiratory failure due to neuromuscular diseases, thoracic restrictive diseases, chronic obstructive pulmonary diseases (COPD), or other lung diseases (cystic fibrosis, bronchiectasis)?

a. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements (e.g., reduction in hypercapnia) considered for the initiation and continuation of noninvasive positive pressure mechanical ventilation supplied by a HMV through a noninvasive interface in the home?

b. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements (e.g., reduction in hypercapnia) considered for the initiation and continuation of noninvasive positive pressure ventilation supplied as a BPAP through a noninvasive interface in the home?

c. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements (e.g., reduction in hypercapnia) considered for the initiation and continuation of noninvasive positive pressure ventilation supplied as a CPAP through a noninvasive interface in the home?

KQ2. In each of the above groups, what is the effect of HMV, a BPAP, or a CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

KQ3. What are the equipment parameters that are used in each of the above groups?

a. What are the parameters of ventilator usage (e.g., mode as determined by trigger, control and cycling variables)?

b. What are the equipment parameters that are necessary to achieve desired outcomes (e.g., flow capabilities, settings, etc.)?

c. What are the parameters of prescribed patient usage (e.g., frequency of use, duration of use throughout the day, other)?
In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?

KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g., patient education, ongoing smoking cessation, respiratory therapist led home care)?

KQ5. What are the professional guidelines and statements that address KQ 1 to KQ 4?

Methods

We followed the established methodologies of systematic reviews as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Comparative Effectiveness Reviews. The study protocol is registered in the international prospective register of systematic reviews (PROSPERO #: CRD42018085676) and published on the AHRQ Web site (https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/topicrefinement/hmv-protocol.pdf). The full report details our literature search strategy, inclusion and exclusion criteria, and data synthesis. We also discuss our assessments of risk of bias and strength of evidence.

Glossary of Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive mechanical ventilation</td>
<td>Delivery of mechanical ventilation through a permanent interface such as tracheostomy (not covered in this report).</td>
</tr>
<tr>
<td>Noninvasive positive pressure ventilation (NIPPV)</td>
<td>Delivery of mechanical ventilation through a temporary interface such as a tight fitting mask.</td>
</tr>
<tr>
<td>Continuous positive airway pressure (CPAP)</td>
<td>A machine that delivers a single level of positive airway pressure throughout the entire respiratory cycle (inspiration and expiration).</td>
</tr>
<tr>
<td>Bi-level positive airway pressure (BPAP)</td>
<td>A machine that delivers two levels of positive airway pressure. On inspiration, the machine delivers an inspiratory positive airway pressure (IPAP). On expiration, the machine delivers an expiratory positive airway pressure (EPAP). BPAP devices may also be referred to as respiratory assist devices (RADs).</td>
</tr>
<tr>
<td>Home mechanical ventilator (HMV)</td>
<td>A machine capable of delivering pressure and/or volume targeted ventilation outside of the hospital setting. HMVs are usually the machine of choice for patients with tracheostomy, but may also be used in patients via a noninvasive interface. Compared to BPAP machines, HMVs typically have additional monitoring, ventilator control, safety, and backup power features. HMVs are classified by the United States Food and Drug Administration (FDA) as &quot;life support devices.&quot;</td>
</tr>
<tr>
<td>HMV/BPAP mix</td>
<td>Cohorts where part of the cohort used NIPPV via a HMV device, part of the cohort used NIPPV via a BPAP device, and outcomes were only reported for the combined cohort.</td>
</tr>
<tr>
<td>BPAP S (spontaneous)</td>
<td>All breaths are initiated by patient effort (spontaneous breaths).</td>
</tr>
<tr>
<td>Term</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>BPAP ST (spontaneous/timed)</td>
<td>In addition to breaths initiated by patient effort, a backup respiratory rate is set to ensure a minimum number of breaths per minute.</td>
</tr>
<tr>
<td>BPAP volume assured pressure support</td>
<td>The machine monitors and automatically adjusts the levels of pressure support to achieve an average target tidal volume.</td>
</tr>
<tr>
<td>Pressure support ventilation</td>
<td>The machine delivers air at a preset inspiratory pressure. The duration of each breath and the respiratory rate are determined by patient effort.</td>
</tr>
<tr>
<td>Pressure control ventilation</td>
<td>The machine delivers a preset inspiratory pressure. The duration of each breath and the respiratory rate are preset. Tidal volume may vary.</td>
</tr>
<tr>
<td>Volume control ventilation</td>
<td>The machine delivers a preset tidal volume and respiratory rate. Tidal volume is fixed regardless of patient effort.</td>
</tr>
<tr>
<td>Assist control</td>
<td>Patients can initiate spontaneous breaths above the preset respiratory rate. Breath delivery may be volume or pressure controlled.</td>
</tr>
</tbody>
</table>

Abbreviations and Acronyms are listed at the end of this Evidence Summary and on page 70 of the Main Report.

**Results**

The literature search identified 6,097 citations, with 63 additional citations identified through reference mining, grey literature search, Key Informants, and public comments. We included 61 original studies with a total of 53,414 patients in the systematic review. Studies were conducted in the United States (4), Canada (1), Europe (47), and other locations (9). We also identified 13 relevant clinical practice guidelines.

**Chronic Obstructive Pulmonary Disease (COPD)**

Thirty-four studies evaluating 51,175 patients were included. Studies evaluated HMV (7), BPAP (30), and CPAP (2) use. Studies were conducted in the United States (4), Canada (1), Europe (24), and other locations (5). We identified eight clinical practice guidelines.

Overall risk of bias in RCTs was rated as moderate to high for issues related to blinding and possible risk of conflicts of interest from study sponsorship. In observational studies, the risk of bias was also high due to the lack of clarity about patient selection methods, prognostic balance, and the unknown conflicts of interest.

**Initiation Criteria for COPD (KQ1):**

The criteria used to start NIPPV were variable but most commonly included: FEV1 <50% of normal, PaCO2 >45mmHg, pH >7.35, and/or hypoxia.

NIPPV was initiated in patients with stable COPD or in patients after hospitalization for AECOPD.

No studies compared the initiation criteria among different devices (HMV vs. BPAP vs. CPAP).

Processes used to titrate NIPPV were variable and used the following targets: reduction in hypercapnia, reduction in hypoxia, achievement of target tidal volumes, and reduction in patient symptoms.
Device Effectiveness for COPD (KQ2):

BPAP (compared with no device) was associated with significantly lower mortality (SOE: moderate), need for intubation (SOE: moderate), hospital admissions (SOE: low), and no change in quality of life (SOE: insufficient).

HMV (compared individually with BPAP, CPAP, or no device) was associated with significantly fewer hospital admissions (SOE: low).

Stratified analysis based on disease stability showed that in patients with stable COPD, BPAP (compared with no device) was associated with significantly lower mortality, higher activities of daily living, and reduced dyspnea. In patients with a recent exacerbation, BPAP (compared with no device) was associated with significantly reduced need for intubation.

Device Characteristics for COPD (KQ3):

For BPAP devices, the modes utilized were BPAP spontaneous [S], BPAP spontaneous/timed [ST], BPAP volume assured pressure support ventilation, and pressure controlled ventilation.

For HMV devices, the modes utilized were pressure support ventilation and pressure controlled ventilation.

For CPAP devices, modes were not specified.

Prescribed device usage per day varied from ≥5-12 hours. Actual mean device usage per day ranged from 4.5-9.0 hours.

Respiratory Services for COPD (KQ4):

Evidence is lacking to determine the effect of specific respiratory home services on outcomes.

Respiratory services provided in the home included: telephone hotline staffed by nurses, scheduled phone calls by respiratory therapists, home visits by respiratory therapists, smoking cessation, and a comprehensive home care program with evaluation and treatment of physical, occupational, and dietary needs.

For all conditions, information related to clinical guidelines (KQ5) can be found in Appendix Table G.2 of the full report.

Thoracic Restrictive Diseases

Seven studies evaluating 202 patients were included. Studies evaluated HMV (5) and BPAP (3) use. Studies were conducted in Europe (6), and one other location. We identified six clinical practice guidelines.

Overall risk of bias of the included studies was rated as moderate due to unclear conflict of interest (62.5%) and inadequate followup (37.5%) in the observational studies.

Initiation Criteria for Thoracic Restrictive Diseases (KQ1):

The criteria used to start NIPPV were variable and most commonly included: PaCO2 >45mmHg, FVC<40% or MIP <60cmH2O or nocturnal SaO2 < 88% for ≥ 5 consecutive minutes.
All studies enrolled patients with stable disease (not in acute respiratory failure).
No studies compared the initiation criteria between different devices or evaluated criteria for device continuation.
Processes used to titrate NIPPV were variable and used the following targets: reduction in hypercapnia, reduction in hypoxia, achievement of target tidal volumes, and reduction in patient symptoms.

**Device Effectiveness for Thoracic Restrictive Diseases (KQ2):**
HMV (compared with no device) was associated with lower mortality (SOE: low).
No studies compared outcomes between HMV and BPAP devices.

**Device Characteristics for Thoracic Restrictive Diseases (KQ3):**
For BPAP devices, the modes utilized were BPAP ST and BPAP NOS (unclear which mode).
For HMV devices, the modes utilized were pressure controlled ventilation, volume assist controlled ventilation, and volume/pressure cycled NOS.
Prescribed usage included ≥7 hours/day. Actual mean device usage per day ranged from 6.0-7.3 hours.

**Respiratory Services for Thoracic Restrictive Diseases (KQ4):**
Evidence is lacking to determine the effect of specific respiratory home services on outcomes.
Respiratory services provided in the home included: telephone hotline.

**Neuromuscular Disease (NMD)**
Thirteen studies evaluating 1,015 patients were included. Studies evaluated HMV (4) and BPAP (11) use. Studies were conducted in the Europe (12), and one other location. We identified 10 clinical practice guidelines.
Overall risk of bias was rated as moderate to high for issues related to blinding, risk of allocation concealment, and outcome reporting in the RCT and unknown conflict of interest and high risk of outcome assessment in observational studies.

**Initiation Criteria for Neuromuscular Disease (KQ1):**
The criteria used to start NIPPV were variable and most commonly included: PaCO2 >45mmHg) or FVC<50% or MIP <60cmH2O, or nocturnal SaO2 < 88% for ≥ 5 consecutive minutes.
No studies compared the initiation criteria between different devices or evaluated criteria for device continuation.
Processes used to titrate NIPPV were variable and used the following targets: reduction in hypercapnia, reduction in hypoxia, and reduction in patient symptoms.
Device Effectiveness for Neuromuscular Disease (KQ2):
BPAP (compared with no device) was associated with lower mortality (SOE: low), better quality of life (SOE: low).

Device Characteristics for Neuromuscular Disease (KQ3):
For BPAP devices, the modes utilized were BPAP ST and BPAP NOS (unclear if S or ST)
For HMV devices, the modes utilized were pressure support and volume assist controlled ventilation.
Prescribed device usage per day varied from ≥4–7 hours. Actual mean device usage per day ranged from 3.8–9.3 hours.

Respiratory Services for Neuromuscular Disease (KQ4):
Respiratory services provided in the home included: telephone hotline, scheduled phone calls, and cough assistance including mechanical cough assist devices provided by a respiratory therapist.
Weekly telemonitoring was associated with significantly lower rates of office visits, ER visits, and hospital admission, with no change in mortality.

Obesity Hypoventilation Syndrome
Nine studies\textsuperscript{42, 47, 51, 65-70} evaluating 577 patients were included. Studies evaluated HMV (3) \textsuperscript{47, 51, 67}, BPAP (8) \textsuperscript{42, 65-70}, and CPAP (3) \textsuperscript{65, 67, 70} use. Studies were conducted in Europe (6) and three other locations. We identified five clinical practice guidelines.
Overall risk of bias was rated as moderate for issues related to blinding and risk of conflicts of interest in the RCT and selective patient population in observational studies.

Initiation Criteria for Obesity Hypoventilation Syndrome (KQ1):
The criteria used to start NIPPV were variable but most commonly included: BMI >30kg/m\textsuperscript{2}, PaCO\textsubscript{2}>45mmHg, and other causes of hypercapnia ruled out.
No studies compared the initiation criteria among different devices or evaluated criteria for device continuation.
Processes used to titrate NIPPV were variable and used the following targets: reduction in hypercapnia, reduction in hypoxia (including nocturnal hypoxia), achievement of target tidal volumes, and reduction in patient symptoms.

Device Effectiveness for Obesity Hypoventilation Syndrome (KQ2):
HMV/BPAP mix (compared with no device) showed no difference in quality of life (SOE: insufficient).
HMV/BPAP mix (compared with CPAP) showed no difference in quality of life (SOE: insufficient).
CPAP (compared with no device) showed no difference in quality of life (SOE: insufficient).
BPAP (compared with CPAP) showed no differences in hospital admissions (SOE: insufficient), or quality of life (SOE: insufficient).
**Device Characteristics for Obesity Hypoventilation Syndrome (KQ3):**

For BPAP devices, the modes utilized were BPAP ST, BPAP S, and BPAP NOS (unclear if S or ST).

For HMV devices, the modes utilized were volume/pressure cycled NOS, pressure support and pressured controlled ventilation as well as a mixture of bilevel BPAP/HMV each with assured volume modes.

**Respiratory Services for Obesity Hypoventilation Syndrome (KQ4):**

Evidence is lacking to determine the effect of home-based lifestyle counseling by nurses.

---

**Other Respiratory Diseases**

Other respiratory diseases included cystic fibrosis, bronchiectasis, and interstitial lung disease. Two studies\(^{42, 71}\) evaluating 42 patients were included. Studies evaluated HMV (1) \(^{71}\) and BPAP (1) \(^{42}\) use. One study was conducted in Europe and one in another location. We identified three clinical practice guidelines.

Overall risk of bias was rated as moderate due to selective patient population and unclear risk of conflict of interest in the observational studies.

**Initiation Criteria for Other Respiratory Diseases (KQ1):**

The criteria used to start NIPPV were variable but most commonly included: diagnosis of diffuse parenchymal lung disease and/or bronchiectasis, hypoxia, and/or hypercapnia.

No studies compared the initiation criteria between different devices or evaluated criteria for device continuation.

Processes used to titrate NIPPV were variable with the following targets used: reduction in hypercapnia, reduction in hypoxia (including nocturnal hypoxia), and achievement of target tidal volumes.

**Device Effectiveness for Other Respiratory Diseases (KQ2):**

Mortality, hospital admission, quality of life, or need for intubation was not evaluated.

HMV (compared with no device) was associated with significantly shorter length of hospital stay in patients with bronchiectasis.

**Device Characteristics for Other Respiratory Diseases (KQ3):**

The BPAP mode utilized was BPAP ST. The HMV mode utilized was volume assist control ventilation mode.

**Respiratory Services for Other Respiratory Diseases (KQ4):**

No studies described respiratory services provided in the home.
Mixed Disease Conditions

Mixed disease conditions included cohorts of patients with one or more of the above described disease conditions. Five studies\textsuperscript{34,72-75} evaluating 331 patients were included. Studies evaluated HMV (4)\textsuperscript{34,72,73,75} and BPAP (1)\textsuperscript{74} use. Studies were conducted in Europe (4) and one in another location. We identified six clinical practice guidelines.

Overall risk of bias was rated as moderate. The RCTs were unable to blind patients, providers, or outcome assessors, and had unclear risk of allocation concealment. The observational studies were found to have selective patient population, and high risk of outcome assessment.

Initiation Criteria for Mixed Disease Conditions (KQ1):

The criteria used to start NIPPV were variable but most commonly included PaCO\textsubscript{2}>45mmHg, hypoxia, and/or pH ≥7.35.

HMV started in the home setting compared to HMV started in the hospital was not associated with differences in mortality or quality of life (in patients with NMD or TRD).

No major differences were found in the criteria used to initiate a BPAP or a HMV device.

Processes used to titrate NIPPV were variable with the following targets used: reduction in hypercapnia, reduction in hypoxia, and achievement of target tidal volumes.

Device Effectiveness for Mixed Disease Conditions (KQ2):

BPAP (compared with no device) was associated with reduced hospital admissions (SOE: low) in patients with COPD, asthma, or bronchiectasis.

Device Characteristics for Mixed Disease Conditions (KQ3):

BPAP devices used mode BPAP NOS (unclear if S or ST)

For HMV devices, the modes utilized were pressure controlled ventilation, volume assist control ventilation, volume control ventilation, and pressure/volume controlled ventilation NOS.

Respiratory Services for Mixed Disease Conditions (KQ4):

Evidence is lacking to determine the effect of telephone hotline and scheduled phone calls on outcomes.

Adverse Events

Only 19 out of the 61 included studies (31.15\%) evaluated adverse events. A majority of these studies did not use a consistent approach for evaluation and reporting.

Serious events (such as mortality, hospitalization, and need for intubation) were commonly classified as study outcomes and were infrequently and non-uniformly classified as serious adverse events.

The pooled incidence of reported non serious adverse events was 0.35 for HMV, 0.31 for BPAP, 0.27 for HMV/BMPAP mix, 0.39 for CPAP, and <0.001 for no device groups.

The pooled incidence of reported serious adverse events was <0.001 for HMV, 0.01 for BPAP, 0.09 for CPAP, and <0.001 for no device groups.
Based on direct comparison, we found no statistically significant differences in total number of treatment withdrawals or adverse events (serious plus other) when comparing different devices or when comparing device use with no device use.

Discussion

We conducted a systematic review to assess the effectiveness of home NIPPV (using HMV, BPAP, and/or CPAP devices) in adults with chronic respiratory failure. We assessed the criteria considered for initiation and continuation, respiratory services provided in the home, adverse events, and summarized relevant clinical practice guidelines. Regarding outcomes associated with device use, overall, we found only two studies that directly compared an HMV device with a BPAP device (one study in COPD and one study in NMD).

When evaluating patients with chronic respiratory failure who may benefit from NIPPV in the home setting, key clinical considerations include 1) when to start NIPPV and 2) which device type (HMV vs. BPAP) and device mode are needed to deliver acceptable and safe ventilation. These considerations may vary based on the underlying etiology of chronic respiratory failure (COPD vs. thoracic restrictive disease vs. neuromuscular diseases vs. obesity hypoventilation vs. other). In general, included studies evaluated the efficacy of starting chronic home NIPPV in patients with moderate to severe stable disease and/or patients with unstable disease in current acute respiratory exacerbation.

The following tables summarize the findings by condition, device, and comparator.

### Table 1. Summary of device effectiveness in patients with COPD

<table>
<thead>
<tr>
<th>Device</th>
<th>Comparator(s)</th>
<th>Findings (Strength of evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMV</td>
<td>Individually with BPAP, CPAP, or no device</td>
<td>Fewer hospital admissions (low SOE)</td>
</tr>
<tr>
<td>HMV</td>
<td>no device</td>
<td>No difference in mortality (insufficient SOE)</td>
</tr>
<tr>
<td>BPAP</td>
<td>no device</td>
<td>Lower mortality (moderate SOE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced need for intubation (moderate SOE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fewer hospital admissions (low SOE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No difference in quality of life (insufficient SOE)</td>
</tr>
<tr>
<td>BPAP volume assured pressure support ventilation</td>
<td>BPAP ST</td>
<td>No difference in mortality (insufficient SOE) and quality of life (insufficient SOE)</td>
</tr>
<tr>
<td>HMV pressure controlled ventilation</td>
<td>HMV pressure support ventilation</td>
<td>No difference in quality of life (insufficient SOE)</td>
</tr>
</tbody>
</table>

BPAP: bilevel positive airway pressure, CPAP: continuous positive airway pressure, HMV: home mechanical ventilator, ICU: intensive care unit, SOE: strength of evidence, ST: spontaneous/timed mode

### Table 2. Summary of device effectiveness in patients with thoracic restrictive diseases

<table>
<thead>
<tr>
<th>Device</th>
<th>Comparator(s)</th>
<th>Findings (Strength of evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMV</td>
<td>no device</td>
<td>Lower mortality (low SOE)</td>
</tr>
</tbody>
</table>

HMV: home mechanical ventilator, SOE: strength of evidence

### Table 3. Summary of device effectiveness in patients with neuromuscular disease

<table>
<thead>
<tr>
<th>Device</th>
<th>Comparator(s)</th>
<th>Findings (Strength of evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAP</td>
<td>no device</td>
<td>Lower mortality (low SOE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Better quality of life (low SOE)</td>
</tr>
</tbody>
</table>

BPAP: bilevel positive airway pressure, HMV: home mechanical ventilator, SOE: strength of evidence
Table 4. Summary of device effectiveness in patients with obesity hypoventilation syndrome

<table>
<thead>
<tr>
<th>Device</th>
<th>Comparator(s)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMV/BPAP mix</td>
<td>no device</td>
<td>No difference in exercise tolerance or quality of life (insufficient SOE)</td>
</tr>
<tr>
<td>HMV/BPAP mix</td>
<td>CPAP</td>
<td>No difference in sleep quality or quality of life (insufficient SOE)</td>
</tr>
<tr>
<td>CPAP</td>
<td>no device</td>
<td>No difference in exercise tolerance or quality of life (insufficient SOE)</td>
</tr>
<tr>
<td>BPAP</td>
<td>CPAP</td>
<td>No difference in hospital admissions (insufficient SOE), and quality of life (insufficient SOE)</td>
</tr>
</tbody>
</table>

BPAP: bilevel positive airway pressure, CPAP: continuous positive airway pressure, HMV: home mechanical ventilator, SOE: strength of evidence.

Table 5. Summary of device effectiveness in patients with other respiratory diseases

<table>
<thead>
<tr>
<th>Device</th>
<th>Comparator(s)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMV</td>
<td>no device</td>
<td>Mortality, hospital admission, quality of life, or need for intubation was not evaluated. Shorter length of hospital stay</td>
</tr>
</tbody>
</table>

HMV: home mechanical ventilator, SOE: strength of evidence. Other respiratory diseases included cystic fibrosis, bronchiectasis, and interstitial lung disease.

Table 6. Summary of device effectiveness in patients with mixed disease conditions

<table>
<thead>
<tr>
<th>Device</th>
<th>Comparator(s)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAP</td>
<td>no device</td>
<td>Fewer hospital admissions (low SOE)</td>
</tr>
</tbody>
</table>

BPAP: bilevel positive airway pressure, SOE: strength of evidence. Mixed disease conditions included cohorts of patients with one or more of COPD, thoracic restrictive diseases, neuromuscular disease, obesity hypoventilation syndrome, or other respiratory diseases.

We found no major differences in the criteria considered for initiation of a HMV versus BPAP device—and included studies did not directly address this clinical question. The most common criteria for initiation of home NIPPV using a HMV and/or BPAP device were 1) COPD (FEV1<50% normal, PaCO2 >45mmHg, pH>7.35, and/or hypoxia), 2) thoracic restrictive diseases (PaCO2>45mmHg, stable disease, and FVC<40% normal or MIP<60cmH2O, or nocturnal SaO2<88% for ≥ 5 consecutive minutes), 3) neuromuscular disease (PaCO2>45mmHg or FVC<50% or MIP <60cmH2O, or nocturnal SaO2 < 88% for ≥ 5 consecutive minutes), 4) obesity hypoventilation syndrome (BMI>30kg/m2, PaCO2>45mmHg, and other causes of hypercapnia ruled out), 5) other respiratory diseases (hypercapnia and hypoxia).

Respiratory services provided in the home were variable and included: telephone hotline, scheduled phone calls, home visits, smoking cessation, cough assistance instruction and devices, and dietary and lifestyle counseling. Only one RCT evaluated the efficacy of home respiratory services and found that BPAP ST with weekly telemonitoring (compared with BPAP ST alone) in NMD patients was associated with fewer office visits, fewer emergency room visits, fewer hospital admissions, and no difference in mortality.

Serious and non-serious adverse events were reported in patients in the HMV, BPAP, CPAP, and no device groups. Incidence rate of non-serious adverse events (such as facial rash, mucosal dryness, mask discomfort, etc.) was around 0.3. Reported serious adverse events were rare. The most commonly reported serious adverse event was acute respiratory failure, which occurred in patients using BPAP, CPAP, as well as patients using no devices. The recognition that patients using NIPPV devices may experience serious adverse events such as acute respiratory failure should be interpreted with the following considerations: First, reporting of serious adverse events was not uniform across studies, with a majority of studies not reporting serious adverse events and a majority of the remaining studies reporting no serious adverse events. Second, many studies that reported serious adverse events such as acute respiratory failure in patients who used
NIPPV devices also reported that acute respiratory failure occurred, sometimes at even higher rates, in patients who used no devices. Third, outcomes such as death, hospitalization, and need for intubation were considered as primary efficacy outcomes and not serious adverse events. Therefore, recognition of serious adverse events should be balanced with efficacy data showing benefit in mortality, hospitalization, and need for intubation in many disease categories. Fourth, comparative studies found no statistically significant differences in adverse events or treatment withdrawals among device type.

Findings in Relation to What Is Known

This systematic review provides evidence that in patients with nearly every disease condition, NIPPV was associated with both a statistically and clinically significant reduction in mortality. In addition, in patients with COPD, NIPPV was associated with fewer hospitalizations, fewer intubations, reduced dyspnea and no change in quality of life. In COPD, NIPPV via HMV (compared individually to BPAP, CPAP, or no device) was associated with fewer hospital admissions (SOE: low). For patients with TRD, NMD, OHS, and other lung diseases, NIPPV was also associated with improved exercise tolerance, improved quality of life, reduced dyspnea, improved sleep quality, and shorter length of hospital stay in individual populations. Published guidelines varied with regards to criteria used to start NIPPV, criteria used to titrate NIPPV, recommended equipment parameters to use in specific disease conditions, and recommended respiratory services, all with various levels of evidence. While many guidelines recommended initiation of home NIPPV for daytime hypercapnia (PaCO2 ≥ 45mmHg), some guidelines recommended initiation of home NIPPV prior to the development of daytime hypercapnia. In COPD, some guidelines recommend initiation of home NIPPV in patients with chronic daytime hypercapnia and/or recurrent episodes of acute hypercapnic respiratory failure, some guidelines cite insufficient evidence to recommend such practices.

While some guidelines recommended certain clinical circumstances when provision of an HMV was preferred to a BPAP machine, there is currently not convincing comparative evidence to support these recommendations. For example, two European guidelines recommended an HMV device with an alternative backup power source, alarms to signal “mask off” or “low pressure” or “power failure,” and a second backup ventilator for patients with any disease condition whose device use approached >16 or >18 hours/day. Guidelines also recommend the volume controlled or volume cycled features of HMV machines when pressure controlled ventilation failed to prevent hypercapnia in NMD, TRD, and OHS and when patients with any condition had difficulty triggering inspiration. Our review also found significant heterogeneity in the specific patient characteristics used to initiate home NIPPV. While most studies used hypercapnia (commonly, but not always defined as PaCO2 ≥ 45mmHg) as one criteria to initiate home NIPPV, there were several other disease specific and variable criteria used to initiate home NIPPV. We found no existing comparative evidence to support guideline recommendations of using HMV when device use approached >16 hours/day.

Limitations

Despite conducting a comprehensive literature search, we were unable to find sufficient evidence to identify ideal criteria to initiate and continue home NIPPV via different devices (KQ1), optimized equipment settings (KQ3), or impact of home respiratory services (KQ4). Qualitative syntheses of these KQs were also limited by heterogeneity of the included studies (population, inclusion/exclusion criteria, targets and process of device titration, devices used,
follow up length, length of use of device, and study design). Our findings were also limited by lack of standard reporting of the following characteristics: 1) device type (i.e., difficulty in differentiating HMV from BPAP), 2) device used (e.g., manufacturer and model), 2) key device characteristics (e.g., mode used), and 3) device titration protocol and targets. For effectiveness and adverse events of home NIPPV (KQ2), the majority of the studies evaluated BPAP and no device in stable COPD patients. The evidence for comparative effectiveness of different devices and different modes is scarce, as well as the evidence for conditions other than stable COPD (i.e., COPD after recent exacerbation, OHS, NMD, or TRD, etc). The evaluation of adverse events was also limited by the fact that most of the included studies did not evaluate adverse events and majority of the rest did not use a consistent approach for report and evaluation. We could not statistically evaluate publication bias because the number of studies included in a direct comparison was small (n<10). We judged included studies to have medium to high risk of bias because of possible conflicts of interests (i.e., funded by device manufacturers), lack of blinding in RCTs and lack of representativeness of patient population in observational studies.

**Applicability**

Several issues limit the applicability of the stated findings. First, included studies were conducted in various locations across the globe. The provision of home NIPPV in different countries may differ based on devices available, devices commonly used, titration protocols, guidelines for home device use, associated respiratory services included, and coverage/payment of home NIPPV. In addition, the classification of devices as either an HMV and/or BPAP machine may differ in the United States compared with other locations. Second, several devices used in the included studies were not FDA approved. Third, several devices used in the included studies were older models that may no longer be available. Fourth, there is no data on several newer devices developed in the past 5-10 years. Fifth, patients in randomized controlled trials may significantly differ from those encountered in practice.

**Suggestions for Future Research**

Future comparative research should define which patient populations would benefit from NIPPV delivered by a HMV compared to a BPAP device. Populations that may benefit from a HMV include patients who require daytime NIPPV for a certain number of hours, patients with continued hypercapnia despite maximal BPAP use, patients who have rapidly progressively disease, or patients who have experienced adverse events despite BPAP use. Such populations may benefit from the tighter ventilator parameters, modes, monitoring, alarm features, and a second back up ventilator as offered by use of an HMV device. Such evidence would improve clinician ability to determine which features and device types are optimal for specific patient populations. In addition, future comparative research should evaluate when to initiate NIPPV, especially evaluating the utility of starting NIPPV in patients with stable disease versus following an episode of acute decompensation. Furthermore, comparative research should define which patient populations would benefit from advanced BPAP modes such as volume assured pressure support compared with other BPAP modes. There is a need to determine the optimal targets and process of device titration.
Conclusion

In COPD, home BPAP (compared to no device) was associated with lower mortality, intubations, hospital admissions, and dyspnea. There was no change in quality of life (pooled analysis of 9 studies). HMV (compared individually with BPAP, CPAP, or no device) was associated with fewer hospital admissions. In thoracic restrictive diseases, home HMV (compared to no device) was associated with lower mortality and better exercise tolerance. In neuromuscular diseases, home BPAP (compared to no device) was associated with lower mortality, better quality of life, and reduced dyspnea. Current comparative evidence is not available to assess the impact of many device capabilities on patient outcomes. Criteria to initiate home NIPPV and home respiratory services vary and are not validated in comparative studies.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ADL</td>
<td>Activities of daily living</td>
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<tr>
<td>AHRQ</td>
<td>Agency for Healthcare Research and Quality</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BPAP</td>
<td>Bi-level positive airway pressure</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
</tr>
<tr>
<td>EPAP</td>
<td>Expiratory positive airway pressure</td>
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<tr>
<td>EPC</td>
<td>Evidence-based Practice Center</td>
</tr>
<tr>
<td>ER</td>
<td>Emergency room</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forced expiratory volume in one second</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>HMV</td>
<td>Home mechanical ventilators</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IPAP</td>
<td>Inspiratory positive airway pressure</td>
</tr>
<tr>
<td>Kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>KQ</td>
<td>Key Question</td>
</tr>
<tr>
<td>m</td>
<td>meters</td>
</tr>
<tr>
<td>MIP</td>
<td>Maximal inspiratory pressure</td>
</tr>
<tr>
<td>mmHg</td>
<td>Millimeters of mercury</td>
</tr>
<tr>
<td>NIPPV</td>
<td>Non-invasive positive pressure ventilation</td>
</tr>
<tr>
<td>NMD</td>
<td>Neuromuscular diseases</td>
</tr>
<tr>
<td>NOS</td>
<td>Not otherwise specified</td>
</tr>
<tr>
<td>OHS</td>
<td>Obesity hypoventilation syndrome</td>
</tr>
<tr>
<td>PaCO2</td>
<td>Partial pressure of arterial carbon dioxide</td>
</tr>
<tr>
<td>pH</td>
<td>Potential of hydrogen</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RADS</td>
<td>Respiratory assist devices</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>S</td>
<td>Spontaneous mode</td>
</tr>
<tr>
<td>SaO2</td>
<td>Arterial blood oxygen saturation</td>
</tr>
<tr>
<td>SOE</td>
<td>Strength of evidence</td>
</tr>
<tr>
<td>ST</td>
<td>Spontaneous/timed breath mode</td>
</tr>
<tr>
<td>TRD</td>
<td>Thoracic restrictive diseases</td>
</tr>
</tbody>
</table>
References


Introduction

Background

Chronic respiratory failure is a common medical condition characterized by the inability to maintain normal oxygen (PaO$_2$ ≥ 60mmHg) and/or carbon dioxide (PaCO$_2$ ≤ 45mmHg) levels. Many diseases may lead to chronic respiratory failure including chronic obstructive pulmonary disease (COPD), thoracic restrictive diseases (TRD) such as kyphoscoliosis, neuromuscular diseases (NMD), and obesity hypoventilation. Associated with increased morbidity and mortality, chronic respiratory failure may range from mild to severe and may be stable or progressive.

Chronic respiratory failure is treated with chronic mechanical ventilation. Mechanical ventilator devices are broadly classified into two categories: home mechanical ventilators (HMV) and bi-level positive airway pressure (BPAP) devices. While both HMV and BPAP devices provide positive pressure ventilation, their technical features may vary considerably. Variability includes: interface (tracheostomy or mask), mode of ventilation (such as pressure targeted versus volume targeted), respiratory circuit (such as single-limb versus double-limb), monitoring capability, safety and alarm systems, and internal battery life. Devices also differ by level of oversight and servicing.

If deemed to be feasible and safe, using these devices in the home setting is preferred to other settings such as intensive care units (ICUs), ventilator weaning units, or long-term care hospitals. Advantages of home use include lower costs, greater independence, increased quality of life, decreased risk of hospital-acquired infections, and reduced use of acute care facilities. The number of patients using long-term HMVs and BPAP devices is growing.

For patients who use home mechanical ventilation through a noninvasive interface, or noninvasive positive pressure ventilation (NIPPV), selecting the optimal device type (HMV versus BPAP versus continuous positive airway pressure [CPAP]) and device settings is imperative. Depending on the severity of illness, patients with chronic hypercapnic respiratory failure may require no, intermittent, or continuous ventilatory support. Failing to adequately treat chronic respiratory failure with the appropriate device could potentially result in sudden or gradual hypoxemia and/or hypercapnia. This can lead to poor quality of life, sleepiness, hospital admission, intubation, and even respiratory arrest and death.

Currently, substantial variability exists regarding the usage, prescribing patterns, policies, and guidelines among noninvasive HMVs, BPAPs, and CPAPs. While a number of guidelines address home use of BPAPs and HMVs, there is marked variability in the conclusions, recommendations, and evidence basis for these guidelines. With current practice and guideline variability, there is a clear need to synthesize the best available evidence to guide prescribing.

This systematic review evaluates home NIPPV in adult patients with chronic respiratory failure primarily due to chronic obstructive pulmonary disease (COPD), thoracic restrictive disorders, and neuromuscular disease. Other causes of respiratory failure were included due to additional interest.

Scope and Key Questions

Scope of the Review
This systematic review addresses initiation and continuation of home NIPPV including the effectiveness, equipment settings, and related respiratory services for patients with chronic respiratory failure. The systematic review also highlights areas of controversy and identifies needs for future research. NIPPV in other settings were excluded (e.g. long term acute care hospital, skilled nursing facility, etc.)

**Key Questions**

The following Key Questions (KQs) were determined based on input from multiple key informants, Centers for Medicare and Medicaid Services (CMS) and the public (drafted KQs were posted for public comment from November 3rd, 2017 to November 17th, 2017). The related PICOTS (population, interventions, comparisons, outcomes, timing, and setting) are listed in Table 1.

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bilevel Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface for the population of patients with chronic respiratory failure due to neuromuscular diseases, thoracic restrictive diseases, chronic obstructive pulmonary diseases (COPD), or other lung diseases (cystic fibrosis, bronchiectasis)?

   d. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements (e.g., reduction in hypercapnia) considered for the initiation and continuation of noninvasive positive pressure mechanical ventilation supplied by a HMV through a noninvasive interface in the home?

   e. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements (e.g., reduction in hypercapnia) considered for the initiation and continuation of noninvasive positive pressure ventilation supplied as a BPAP through a noninvasive interface in the home?

   f. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements (e.g., reduction in hypercapnia) considered for the initiation and continuation of noninvasive positive pressure ventilation supplied as a CPAP through a noninvasive interface in the home?

KQ2. In each of the above groups, what is the effect of HMV, a BPAP, or a CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

KQ3. What are the equipment parameters that are used in each of the above groups?

   e. What are the parameters of ventilator usage (e.g., mode as determined by trigger, control and cycling variables)?

   f. What are the equipment parameters that are necessary to achieve desired outcomes (e.g., flow capabilities, settings, etc.)?

   g. What are the parameters of prescribed patient usage (e.g., frequency of use, duration of use throughout the day, other)?

   h. In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?
KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g., patient education, ongoing smoking cessation, respiratory therapist led home care)?

KQ5. What are the professional guidelines and statements that address KQ 1 to KQ 4?

Table 1. PICOTS (population, interventions, comparisons, outcomes, timing, and setting)

<table>
<thead>
<tr>
<th>PICOTS Elements</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Populations</td>
<td>Humans</td>
<td>Animals</td>
</tr>
<tr>
<td></td>
<td>Adults 18 years and older</td>
<td>Children (age &lt; 18 years)</td>
</tr>
<tr>
<td></td>
<td>Patients with COPD</td>
<td>Patients in whom the indication for the device was the lone diagnosis of:</td>
</tr>
<tr>
<td></td>
<td>Obesity, obesity hypoventilation syndrome, hypoventilation syndrome</td>
<td>Any sleep apnea (obstructive, central, complex)</td>
</tr>
<tr>
<td></td>
<td>Neuromuscular disease</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>Thoracic cage abnormality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interstitial lung disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cystic fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bronchiectasis</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>Noninvasive mask or mouthpiece:</td>
<td>Mechanical insufflation and exsufflation device / cough assist device</td>
</tr>
<tr>
<td></td>
<td>HMV</td>
<td>High flow nasal cannula oxygen</td>
</tr>
<tr>
<td></td>
<td>BPAP</td>
<td>Negative pressure ventilators</td>
</tr>
<tr>
<td></td>
<td>CPAP</td>
<td>Patients with tracheostomy</td>
</tr>
<tr>
<td>Comparators</td>
<td>Usual care (i.e. no HMV/BPAP/CPAP)</td>
<td>Invasive ventilation (e.g. tracheostomy)</td>
</tr>
<tr>
<td></td>
<td>Different type of noninvasive mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Different modes of same equipment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other noninvasive ventilation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Studies without a comparator treatment that evaluate the effect of a patient characteristic, laboratory criteria, ventilator parameter, or respiratory services on outcomes of interest will be included)</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mortality</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Hospitalization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Admission/readmission to intensive care unit (ICU)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Need for intubation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Outpatient visits</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emergency room visits</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disease exacerbations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quality of life (QoL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Activities of daily living (ADL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep quality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exercise tolerance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adverse events</td>
<td></td>
</tr>
<tr>
<td>Timing</td>
<td>At least 1 month of treatment in home settings</td>
<td>None</td>
</tr>
<tr>
<td>Settings</td>
<td>Therapy (BPAP, CPAP, HMV) administered and studied at home or assisted living. Therapy could have been started at hospital / ICU but must be evaluated in the study as an outpatient treatment.</td>
<td>Therapy (BPAP, CPAP, HMV) administered only in:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nursing home/skilled nursing facility (SNF)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Long term acute care facility (LTACH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hospital step down unit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hospital chronic ventilator unit / ventilator weaning unit</td>
</tr>
<tr>
<td>PICOTS Elements</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Study design</td>
<td>Original data</td>
<td><em>In vitro</em> studies</td>
</tr>
<tr>
<td></td>
<td>Any sample size</td>
<td>Non-original data (e.g. narrative</td>
</tr>
<tr>
<td></td>
<td>RCTs, nonrandomized</td>
<td>reviews, editorials, letters, or erratum)</td>
</tr>
<tr>
<td></td>
<td>comparative studies (prospective</td>
<td>Non-comparative observational</td>
</tr>
<tr>
<td></td>
<td>and retrospective)</td>
<td>studies, case series</td>
</tr>
<tr>
<td></td>
<td>Relevant systematic</td>
<td>Qualitative studies</td>
</tr>
<tr>
<td></td>
<td>reviews, or meta-analyses (used for</td>
<td>Cost-benefit analysis</td>
</tr>
<tr>
<td></td>
<td>identifying additional studies)</td>
<td>Cross-sectional (i.e., non-longitudinal)</td>
</tr>
<tr>
<td></td>
<td>Clinical guideline</td>
<td>studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Before-after studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Survey</td>
</tr>
</tbody>
</table>

BPAP: bi-level positive airway pressure, COPD: chronic obstructive pulmonary disease, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, KQ: key question, PICOTS: populations, interventions, comparators, outcomes, timing, and settings, RCT: randomized controlled trial

**Organization of the Report**

In this report, we first presented the methods used to collect, screen, and synthesize the literature. The results section was organized first by disease conditions (chronic obstructive pulmonary disease, thoracic restrictive diseases, neuromuscular disease, obesity hypoventilation syndrome, other lung diseases, and mixed disease conditions) and then by KQs. Adverse events were summarized at the end of the results, regardless of disease conditions. After the results section, we summarized our findings, findings in relation to what is known, limitations, applicability of the findings, future research needs, and conclusion.
Methods

We developed an analytic framework to guide the process of the systematic review (Figure 1). We followed the established methodologies of systematic reviews as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Comparative Effectiveness Reviews. The reporting complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements. The study protocol is registered in the international prospective register of systematic reviews (PROSPERO #: CRD42018085676) and published on the AHRQ Web site (https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/topicrefinement/hmv-protocol.pdf).

Figure 1. Analytic framework

(KQ 5)

What are the professional guidelines and statements which address KQ 1 to KQ 4?

(KQ 1) Clinical characteristics
Patient characteristics, ability to manage device, laboratory criteria, criteria for initiation and continuation of treatment

Patients with chronic respiratory failure due to neuromuscular diseases, thoracic restrictive diseases, interstitial lung disease, chronic obstructive pulmonary disease, or other lung diseases (cystic fibrosis, bronchiectasis)

(KQ 2) Through a noninvasive interface after HMV, BPAP, or CPAP

(KQ 3) Equipment and usage
Device type
Parameters of device usage
Measures to improve compliance

(KQ 4) Respiratory services
Patient education, ongoing smoking cessation, respiratory therapist home care, etc.

(KQ 5) Patient-centered outcomes
Mortality, hospitalization, admission/readmission to ICU, need for intubation, outpatient visits, emergency room visits, disease exacerbations, QoL, ADL, dyspnea, sleep quality, exercise tolerance, and adverse events

Adverse Events
Literature Search Strategy

Search Strategy

We conducted a comprehensive literature search of eight databases, including National Guideline Clearinghouse, Embase, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Cochrane Central Registrar of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus from January 1, 1995 to June 26, 2018. We also searched FDA Establishment Registration & Device Listing, ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency (MHRA), AHRQ’s Horizon Scanning System, conference proceedings, patient advocate group websites, and medical society websites. Relevant clinical guidelines, systematic reviews, and meta-analysis, as well as reference mining of relevant publications, were used to identify additional literature. An experienced librarian, with the help of the study investigators, developed the search strategy (Appendix B) and conducted the search. An independent information specialist peer reviewed the search strategy.

Inclusion and Exclusion Criteria

The eligible studies had to meet all the following criteria: 1) Adults 18 years and older with chronic respiratory failure due to neuromuscular diseases, thoracic restrictive diseases, chronic obstructive pulmonary diseases (COPD), or other lung diseases (cystic fibrosis, bronchiectasis); 2) received noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bilevel Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) through noninvasive interface; 3) received at least 1 month of treatment at home or assisted living; 4) compared with usual care; different type of noninvasive mechanical ventilation, different modes of same equipment, or other noninvasive ventilation; 5) reported patient-centered outcomes, and 6) published after 1995 and in English only. We included randomized controlled trials (RCTs), nonrandomized comparative studies (prospective and retrospective), and clinical guidelines. We did not restrict study location, and sample size. The detailed inclusion and exclusion criteria can be found in Table 1.

Study Selection

Independent reviewers, working in pairs, screened the titles and abstracts of all citations using pre-specified inclusion and exclusion criteria. Studies included by either reviewer were retrieved for full-text screening. Independent reviewers, again working in pairs, screened the full-text version of eligible references. Discrepancies between the reviewers were resolved through discussions and consensus. If consensus could not be reached, a third reviewer resolved the difference.

Data Extraction

We developed a standardized data extraction form to extract study characteristics (author, study design, inclusion and exclusion criteria, patient characteristics, laboratory criteria, intervention, comparisons, outcomes, equipment parameters, respiratory services, and related items for assessing study quality and applicability). The standardized form was pilot-tested by all study team members using 10 randomly selected studies. We iteratively continued testing the
form until no additional items or unresolved questions existed. After we finalized the form, reviewers worked independently to extract study details. A second reviewer reviewed data extraction, and resolved conflicts.

**Assessment of Risk of Bias of Individual Studies**

We evaluated the risk of bias of the included study using predefined criteria. For RCTs, we used the Cochrane Collaboration’s Risk of Bias tool to assess sequence generation; allocation concealment; participant, personnel, and outcome assessor blinding; attrition bias; incomplete outcome data; selective outcome reporting; and other sources of bias (e.g. conflict of interest, imbalance of baseline characteristics). Each domain was rated as high, low, or unclear risk. For observational studies, we selected appropriate items from the Newcastle-Ottawa Scale, including representativeness of the patients, ascertainment of exposure and outcomes, adequacy of followup, and possible conflicts of interest. Each item was rated as high, low, or unclear risk.

**Data Synthesis**

We qualitatively summarized key features/characteristics (e.g. study populations, design, intervention, outcomes, device model, equipment parameters, and conclusions) of the included studies and presented in evidence tables by each disease and device.

Table 2 lists rules we used to categorize HMV device, BPAP device, or CPAP device.

<table>
<thead>
<tr>
<th>Device</th>
<th>Rules</th>
</tr>
</thead>
</table>
| HMV     | 1) The study reported the device model/manufacturer, and the device was classified as a life support ventilator by either the FDA or the manufacturer listed information, or  
         2) The study reported the device to be a life support device, or  
         3) The study reported the device was also able to be used interchangeably with invasive mechanical ventilation through a tracheostomy or endotracheal tube, or  
         4) The study reported the mode to be (or the device was capable of) continuous mandatory ventilation (CMV) in either a pressure controlled PC-CMV (AC-PC) or volume controlled VC- CMV (AC-VC) configuration |
| BPAP    | 1) The study reported the device model/manufacturer, and the device was classified as a BPAP machine or respiratory assist device (RAD) by either the FDA or the manufacturer listed information, or  
         2) The study reported the device to be an exclusive BPAP machine.  
         3) Devices were categorized as BIPAP ST if the mode utilized intermittent mandatory ventilation IMV (back up rate) with pressure support (IPAP) PC-IMV. BIPAP S if breath delivery was continuous spontaneous ventilation CSV with pressure support (IPAP) PC-CSV.                                                                 |
| CPAP    | 1) The study reported the device model/manufacturer, and the device was classified as a CPAP machine either by the FDA or the manufacturer listed information, or  
         2) The study reported the device to be a CPAP machine.                                                                                                                                 |


Adverse events were grouped into adverse events likely due to device use, including 1) mask, tubing (interface) related problems, 2) problems related to nasal route; and 3) pressure, airflow
related problems. All adverse events that were likely not linked to device use were grouped as other adverse events (Table 3).

Table 3. Categories of adverse events

<table>
<thead>
<tr>
<th>Type of adverse events</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>Death, hospitalization, and need for intubation were reported as primary efficacy outcomes.</td>
</tr>
<tr>
<td></td>
<td>Acute respiratory failure</td>
</tr>
<tr>
<td></td>
<td>Any life-threatening event/illness</td>
</tr>
<tr>
<td></td>
<td>Any disability or permanent damage</td>
</tr>
<tr>
<td></td>
<td>Any required intervention to prevent impairment (such as pacemaker)</td>
</tr>
<tr>
<td></td>
<td>Any congenital anomaly/birth defect</td>
</tr>
<tr>
<td>Non serious adverse events</td>
<td>Skin symptoms (e.g. facial rash, nasal ulceration)</td>
</tr>
<tr>
<td></td>
<td>Eye symptoms (e.g. dry eyes, conjunctivitis)</td>
</tr>
<tr>
<td></td>
<td>Nose/mouth symptoms (e.g. nasal stuffiness, rhinorrhea, nosebleed, mucosal dryness, oral air leak)</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal symptoms (e.g. gastric distension, aerophagia)</td>
</tr>
<tr>
<td></td>
<td>Device/mask intolerance (e.g. claustrophobia, discomfort, noncompliance)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
</tbody>
</table>

We conducted meta-analyses to quantitatively combine study findings. All analyses were conducted based on the intention-to-treat principle for RCTs and the number of patients initially assigned to the intervention for observational studies. We calculated odds ratio (OR) and corresponding 95-percent confidence intervals for binary outcomes. For continuous outcomes, we extracted or calculated the difference between post intervention and baseline for each group for all observational studies and for RCTs (whenever possible). When the difference between post intervention and baseline was not presented in RCTs, we extracted post intervention data instead as baseline between groups was typically balanced. When studies used different measures for the same outcome (e.g. Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index for sleep quality), we calculated standardized mean difference (SMD). When studies used the same outcome measure, we used the original scale. For count data (i.e. a patient may have more than one event, e.g. number of hospital admissions), we calculated rate ratio (ratio of the incidence rate of events within a given time between the intervention and the control). For adverse events, we calculated incidence rate by adverse events and type of device. The DerSimonian and Laird random effect method was used except when the number of studies included in the comparison was less than three. The fixed effect model based on the Mantel and Haenszel method was used in that case because of concern about instability of between study variance. We evaluated heterogeneity between studies using I² indicator. Subgroup analysis was only possible when BPAP was compared with no device (stable COPD vs. COPD with recent exacerbation). We were unable to assess publication bias because the number of studies included in the analysis was small (n<20). All statistical analyses were conducted using Stata/SE version 15.1 (StataCorp LLC, College Station, TX).

Grading the Strength of Evidence

We graded the strength of the body of evidence (SOE) as per the EPC methods guide on assessing the strength of evidence. We designated 4 outcomes to be most critical to patients and conducted SOE rating for these major outcomes (mortality, need for intubation, quality of life and all-cause hospital admissions). We produced summary of evidence tables for the major
outcomes that include data source, effect size, SOE rating; and rationale for judgments made on each domain of evidence rating. Other outcomes were either encompassed in these constructs (e.g., symptoms or functional test as a part of quality of life) or were not well ascertained (e.g., cause specific hospitalization). These other outcomes are summarized in tables showing the data source, study type and the effect size.

RCTs start as high SOE and observational studies start as low SOE. We considered the following SOE domains: the methodological limitations of the studies (i.e., risk of bias); precision (based on the size of the body of evidence, number of events, and confidence intervals); directness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs surrogates); consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity); and the likelihood of reporting and publication bias. When confidence intervals were very wide showing substantial benefit and harm and the number of patients was small; we rated SOE as insufficient due to severe imprecision.

Based on this assessment and the initial study design, we assigned a SOE rating as high, moderate, low, or ‘insufficient evidence to estimate an effect’.

Assessing Applicability

We followed the procedures outlined in the EPC Methods Guide for Comparative Effectiveness Reviews to assess the applicability of the findings within and across studies. We focused on whether the populations and interventions in existing studies are representative of current practice. For studies to have good applicability, the devices used in research need to have similar parameters and characteristics to those available in the US at the present time. The characteristics of individuals enrolled in the studies should be similar to typical patients with the targeted conditions described in the PICOTS in terms of disease severity and comorbidities and threshold for being prescribed HMV, BIPAP and CPAP. Patients in the studies should not have excessive home support than what is feasible in real life; otherwise, applicability was judged as limited.

This congruence between research and practice as it relates to applicability was evaluated qualitatively and reported narratively. Research gaps in the topic area were reported in the Discussion.

Peer Review and Public Commentary

A draft report was posted for peer review and public comments between XX and XX. We revised and finalized the draft report in response to comments. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.
Results

Literature Searches and Evidence Base

The literature search identified 6,097 citations. Additional 63 citations were identified through reference missing, grey literature search; and from Key Informants and public comments. 61 original studies with a total of 53,414 patients met inclusion criteria and were included in the systematic review (Appendix Figure A.1.). These studies addressed chronic respiratory failure due to COPD (n=34),6, 15-48 described criteria for initiation of HMV, BPAP, and/or CPAP devices in patients with COPD. Thirty studies6, 15-41, 62-64 neuromuscular diseases (n=10)49, 50, 54-60, thoracic restrictive diseases (n=7)42, 43, 49-53 obesity hypoventilation syndrome (n=9)42, 47, 51, 65-70, or other lung diseases (bronchiectasis, cystic fibrosis, interstitial lung disease, etc.) (n=2)42, 71 5 studies34, 72-75 included patients with mixed conditions and were reported as a separate section. Of these 61 studies, 2031, 34, 38, 43, 45-48, 51-53, 55, 57, 62, 63, 67, 71-73, 75, 82 evaluated HMV, 47 BPAP,6, 15-30, 32, 33, 35-37, 39-42, 44-46, 48-50, 54, 56-61, 63-70, 74, 82 and 5 CPAP.22, 45, 65, 67, 70 Studies were conducted in the United States (n=4), Canada (n=1), Europe (n=47), and other countries (n=9). We also identified 13 relevant clinical practice guidelines. Of these guidelines, eight gave recommendations for COPD,76, 77, 83-88 ten neuromuscular diseases,76, 77, 83, 85, 86, 89-93 six thoracic restrictive diseases,76, 77, 83, 85, 86, 92 five obesity hypoventilation syndrome,76, 77, 83, 85, 86 three other lung diseases,76, 77, 86, 92 and six all diseases in general.76, 77, 83, 85, 86, 92

Figure 2 summarizes the number of studies included per disease condition by device and study design. A list of the studies excluded at the full-text review stage is in Appendix C. A search of ClinicalTrials.gov identified eight ongoing clinical trials.

Figure 2. Number of studies by disease, device, and study design

BPAP: bi-level positive airway pressure, COPD: chronic obstructive pulmonary disease, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, NMD: neuromuscular diseases, RCT: randomized controlled trial, TRD: thoracic restrictive diseases
Chronic Obstructive Pulmonary Disease (COPD)

Thirty-four studies\textsuperscript{6, 15-48} described criteria for initiation of HMV, BPAP, and/or CPAP devices in patients with COPD. Twenty-seven studies\textsuperscript{6, 15-41} with a total of 51,175 patients were included. The characteristics of the studies are listed in Appendix Table D.1. Seven evaluated HMV,\textsuperscript{31, 34, 43, 45-48} thirty BPAP,\textsuperscript{15, 17, 18, 30, 34, 37, 43, 44 6, 15, 16, 19-29, 32, 33, 35, 36, 40-42, 46, 48} and two CPAP.\textsuperscript{18, 22} These studies were conducted in the United States (n=4), Canada (n=1), Europe (n=24), and other countries (n=5). We also identified eight clinical practice guidelines relevant to KQ1-4(Appendix Table G-2).\textsuperscript{76, 77, 83-88}

Overall risk of bias in RCTs was rated as moderate to high due to the inability to blind patients and providers, for not blinding outcome accessors, and for the possible risk of conflicts of interest due to study sponsors (Appendix Table E.1.). In observational studies, the risk of bias was also high due to the same reasons as well as the lack of clarity of patient selection methods and likelihood of prognostic imbalance (Appendix Table E.2).

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bilevel Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface?

Key Points-KQ1

- The criteria used to start NIPPV were variable but most commonly included: FEV1 <50\% of normal, PaCO2 >45mmHg, pH >7.35, and/or hypoxia.
- NIPPV was initiated in patients with stable COPD or in patients after hospitalization for acute exacerbations.
- No studies compared the initiation criteria among different devices (HMV vs. BPAP vs. CPAP).
- Processes used to titrate NIPPV were variable and used the following targets: reduction in hypercapnia, reduction in hypoxia, achievement of target tidal volumes, and reduction in patient symptoms.

No studies directly compared the outcomes of patients based on different criteria of device initiation or compared initiation criteria between different devices (HMV vs. BPAP vs. CPAP).
The following patient and laboratory criteria were used to start home NIPPV using a HMV, BPAP, and or CPAP device:

**FEV1**

Fifteen studies, enrolled patients with FEV1 <50% of normal (GOLD stage III and IV). Other FEV1 cutoff points considered for device use were FEV1 <45%, FEV1 <40%, FEV1 <30%, FEV1 30-49%, and FEV1 <30% or FEV1 <50% plus chronic respiratory failure. FEV1 cutoff points were not specified in 14 studies.

**PaCO2**

Twenty-five studies used PaCO2 measurements for device initiation with varying cutoff levels: PaCO2 >56mmHg, >55mmHg, >53mmHg, >50mmHg, >46mmHg, >45mmHg, and <52mmHg.

**pH**

Eight studies used pH >7.35 for device initiation. One study used pH >7.30, and three studies enrolled patients with pH <7.35.

**PaO2**

Seven studies used hypoxemia as an initiation criteria. Three studies enrolled patients with PaO2 < 60mmHg. One study enrolled patients with PaO2 < 55mmHg (or less than 60mmHg + polycythemia, pulmonary hypertension, or cor pulmonale). Three additional studies enrolled patients on LTOT.

**Stable disease versus recent exacerbation**

Twenty-one studies enrolled patients with stable disease (no recent exacerbation). Eleven studies enrolled patients with recent exacerbation. Two studies enrolled both patients with recent exacerbation and stable disease. One study did not comment on stable disease versus recent exacerbation.

**Other**

Other criteria for initiation of devices include ST90<30%, PtcCo2 >68mmHg.

**Targets of device titration**

Studies reported using maximum tolerated respiratory pressures (such as IPAP and/or EPAP) or other device changes needed to achieve the following goals:

1. Tidal volumes or minute ventilation: tidal volume 6mL/kg measured body weight, tidal volume 7-10mL/kg, tidal volume >8mL/kg, reproduction of daytime minute ventilation at night.
2. Reduction in hypercapnia: maximum reduction in PaCO2, maximum reduction in PtcCO2, PaCO2<45mmHg, PaCO2<49mmHg, 20% reduction in baseline PaCO2, 5% reduction in PaCO2,
3. Reduction in hypoxia: PaO2>60mmHg.
4. Improvement in patient symptoms (reduced respiratory rate, accessory muscle use, dyspnea).\textsuperscript{23, 33}

5. Maximum tolerated IPAP or IPAP/EPAP difference without other identifiable targets.\textsuperscript{20, 24, 27, 36, 37}

6. Set pressures with no titration.\textsuperscript{35}

**Device continuation**

One randomized study of 26 COPD patients reported criteria for device continuation (PaCO\textsubscript{2}>45mmHg) after one night without NIPPV. After 12 months, ten patients (77\%) in the treatment withdrawal group, but only two patients (15\%) in treatment continuation group, experienced clinical worsening (p = 0.0048).\textsuperscript{44}

**KQ2.** What is the effect of HMV, a BPAP, or a CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

**Key Points-KQ2**

- BPAP (compared with no device) was associated with significantly lower mortality (SOE: moderate), need for intubation (SOE: moderate), hospital admissions (SOE: low), and no change in quality of life (SOE: insufficient).
- HMV (compared individually with BPAP, CPAP, or no device) was associated with significantly fewer hospital admissions (SOE: low).
- Stratified analysis based on disease stability showed that in patients with stable COPD, BPAP (compared with no device) was associated with significantly lower mortality, higher activities of daily living, and reduced dyspnea. In patients with a recent exacerbation, BPAP (compared with no device) was associated with significantly reduced need for intubation.

When comparing BPAP to no device (14 RCTs\textsuperscript{6, 18-20, 23, 24, 27-30, 32, 35, 37, 40, 41} and 6 observational studies\textsuperscript{17, 25, 26, 33, 36, 39}), BPAP was associated with significantly better outcomes in terms of mortality (moderate SOE), need for intubation (moderate SOE), number of patients with hospital admissions (low SOE), number of ER admissions, number of patients with ICU admissions, dyspnea, and shuttle walk test. We found no significant difference in other patient outcomes. Comparative effectiveness evidence with SOE rating for major outcomes is summarized in Table 4. Other outcomes are summarized in Table 5. Forest plots are available in Appendix Table H.1.
### Table 4. Major effectiveness outcomes with SOE (BPAP vs. no device in COPD patients)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conclusion</th>
<th>Study Design</th>
<th>Rationale for Strength of Evidence (SOE)</th>
<th>Overall Evidence Strength (Direction of Effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>OR*: 0.66; 95% CI: 0.50 to 0.87; I²=5.9%; 55 fewer per 1000 patients (103 fewer to 8 fewer)</td>
<td>8 RCTs, 6, 19, 20, 23, 27, 29, 32, 40, 41, and 5 Observational studies, 17, 25, 26, 33, 39, 1,423 pts</td>
<td>Risk of bias</td>
<td>Moderate (reduction with BPAP)</td>
</tr>
<tr>
<td>Need for intubation</td>
<td>OR*: 0.34; 95% CI: 0.14 to 0.83; I²=0.0%; 80 fewer per 1000 patients (148 fewer to 13 fewer)</td>
<td>1 RCT, 23 and 2 Observational studies, 17, 33; 267 pts</td>
<td>Risk of bias</td>
<td>Moderate (reduction with BPAP)</td>
</tr>
<tr>
<td>Quality of life (higher score represents better outcome)</td>
<td>SMD*: 0.13, 95% CI: -0.04 to 0.30; I²=65.7%; 8 RCTs, 6, 19, 20, 41, 24, 27-29, 32, and 1 Observational study, 33; 967 pts</td>
<td>Risk of bias and severe imprecision</td>
<td>Insufficient</td>
<td></td>
</tr>
<tr>
<td>Number of hospital admissions</td>
<td>Rate Ratio*: 0.95; 95% CI: 0.90 to 1.01; I²=0.0%; Follow up: 18.5 months</td>
<td>3 RCTs, 23, 32, 40, and 2 Observational studies, 26, 33; 326 pts</td>
<td>Risk of bias and imprecision</td>
<td>Low (reduction with BPAP)</td>
</tr>
<tr>
<td>Number of patients with hospital admissions for respiratory causes</td>
<td>OR: 0.98; 95% CI: 0.56 to 1.71; I²=N/A</td>
<td>1 RCT, 41; 201 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>No significant difference reported on two RCTs, 19, 20; 1 observational study, 1 reported significant reduction (6.6 days vs. 16.0 days, p=0.02)</td>
<td>2 RCTs, 40, 41, and 1 Observational Study, 33; 333 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of ER admissions</td>
<td>Rate Ratio: 0.72; 95% CI: 0.60 to 0.85; I²=N/A; Follow up: 12 months</td>
<td>1 RCT, 39; 195 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of ICU admissions</td>
<td>Rate Ratio*: 0.43; 95% CI: 0.18 to 1.05; I²=0.0%; Follow up: 21 months</td>
<td>1 RCT, 40, and 1 Observational study, 26; 81 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with ICU admissions</td>
<td>OR: 0.18; 95% CI: 0.07 to 0.46; I²=N/A</td>
<td>1 Observational study, 17; 166 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of exacerbations</td>
<td>Rate Ratio*: 0.97; 95% CI: 0.84 to 1.13; I²=0.0%; Follow up: 11.4</td>
<td>3 RCTs, 18-20, 41, and 1 Observational Study, 33; 352 pts</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BPAP: bi-level positive airway pressure, CI: confidence interval, ER: emergency room, ICU: intensive care unit, N/A: not applicable, OR: odds ratio, Pts: patients, RCT: randomized controlled trial, WMD: weighted mean difference.

*: Pooled effect size from meta-analysis

### Table 5. Other effectiveness outcomes (BPAP vs. no device in COPD patients)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conclusion</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with hospital admissions for respiratory causes</td>
<td>OR: 0.98; 95% CI: 0.56 to 1.71; I²=N/A</td>
<td>1 RCT, 41; 201 pts</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>No significant difference reported on two RCTs, 19, 20; 1 observational study, 1 reported significant reduction (6.6 days vs. 16.0 days, p=0.02)</td>
<td>2 RCTs, 40, 41, and 1 Observational Study, 33; 333 pts</td>
</tr>
<tr>
<td>Number of ER admissions</td>
<td>Rate Ratio: 0.72; 95% CI: 0.60 to 0.85; I²=N/A; Follow up: 12 months</td>
<td>1 RCT, 39; 195 pts</td>
</tr>
<tr>
<td>Number of ICU admissions</td>
<td>Rate Ratio*: 0.43; 95% CI: 0.18 to 1.05; I²=0.0%; Follow up: 21 months</td>
<td>1 RCT, 40, and 1 Observational study, 26; 81 pts</td>
</tr>
<tr>
<td>Number of patients with ICU admissions</td>
<td>OR: 0.18; 95% CI: 0.07 to 0.46; I²=N/A</td>
<td>1 Observational study, 17, 166 pts</td>
</tr>
<tr>
<td>Number of exacerbations</td>
<td>Rate Ratio*: 0.97; 95% CI: 0.84 to 1.13; I²=0.0%; Follow up: 11.4</td>
<td>3 RCTs, 18-20, 41, and 1 Observational Study, 33, 352 pts</td>
</tr>
</tbody>
</table>
Two observational studies compared HMV to no device in COPD patients.\textsuperscript{16, 38} There was no significant difference in mortality (OR= 0.56, 95% CI: 0.29 to 1.08). However, patients in the HMV group had significantly less hospital admissions (Rate Ratio= 0.50; 95% CI: 0.35 to 0.71; p<0.01).

A large retrospective study of administrative claims data compared hospital admissions between HMV (315 patients), BPAP (9,156 patients), and CPAP (39,385 patients).\textsuperscript{45} The HMV group were found to have significantly larger reduction of any hospitalization (post-treatment period vs. pre-treatment period) (OR=0.21, 95% CI: 0.15 to 0.30) than those with CPAP (OR=0.67, 95% CI: 0.65 to 0.70) or BPAP (OR=0.40, 95% CI: 0.37 to 0.43) (p<0.001). For COPD-related hospitalization, the HMV group also had significantly larger reduction (OR=0.29, 95% CI: 0.18 to 0.47) than the CPAP group (OR=0.52, 95% CI: 0.47 to 0.59) (p=0.01).

One RCT compared CPAP with BPAP in 49 COPD patients who survived an episode of acute hypercapnic respiratory failure (AHRF).\textsuperscript{22} After a followup of 12 months, 7 out of 23 patients in the BPAP group developed severe COPD exacerbation with AHRF while 14 out of 26 patients in the COPD group had severe exacerbation with AHRF (OR: 0.38, 95% CI: 0.12 to 1.22; p=0.10). 8 patients in the BPAP group withdrew from the study, compared with 4 patients in the CPAP group (OR: 2.93; 95% CI: 0.75 to 11.52; p=0.12).

One RCT compared BPAP volume assured pressure support ventilation to BPAP ST.\textsuperscript{15} The BPAP volume assured pressure support ventilation group had significantly shorter hospital stay than the BPAP ST group (3.3 days vs. 5.2 days, p=0.02). There was no significant difference on mortality (OR=0.47, 95% CI: 0.04 to 5.69; p=0.56), exercise tolerance, dyspnea, quality of life, or sleep quality after 3-month followup.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conclusion</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with exacerbations</td>
<td>OR: 0.84; 95% CI: 0.26 to 2.68; I²=N/A</td>
<td>1 RCT\textsuperscript{23}; 44 pts</td>
</tr>
<tr>
<td>Activities of daily living (ADL) (higher score represents better outcome)</td>
<td>SMD*: 0.08, 95% CI: -0.12 to 0.28; I²=46.7%</td>
<td>3 RCTs\textsuperscript{19, 24, 41}; 318 pts</td>
</tr>
<tr>
<td>Dyspnea (higher score represents better outcome)</td>
<td>SMD*: 0.22, 95% CI: 0.03 to 0.42; I²=44.3%</td>
<td>6 RCTs\textsuperscript{18, 19, 24, 28, 40, 41}; 468 pts</td>
</tr>
<tr>
<td>Sleep quality (higher score represents better outcome)</td>
<td>SMD*:0.0.12; 95% CI: -0.06 to 0.30; I²=0.0%</td>
<td>2 RCTs\textsuperscript{18, 40}; 120 pts</td>
</tr>
<tr>
<td>6-minute walk distance test</td>
<td>WMD*: 23.80 meters; 95% CI: -12.24 to 59.84; I²=55.2%</td>
<td>7 RCTs\textsuperscript{18-20, 28, 30, 35, 37, 40}; 271 pts</td>
</tr>
<tr>
<td>Shuttle walk test</td>
<td>WMD: 72 meters; 95% CI: 12.9 to 131; I²=N/A</td>
<td>1 RCT\textsuperscript{44}; 45 pts</td>
</tr>
</tbody>
</table>

BPAP: bi-level positive airway pressure, CI: confidence interval, ER: emergency room, ICU: intensive care unit, N/A: not applicable, OR: odds ratio, Pts: Patients; RCT: randomized controlled trial, WMD: weighted mean difference.

*: Pooled effect size from meta-analysis
One RCT compared HMV (pressure controlled ventilation) to HMV (pressure support ventilation). There were no significant difference on quality of life (Severe Respiratory Insufficiency Questionnaire Summary Score), and 6-minute walk distance test.

One RCT compared high intensity HMV (pressure controlled ventilation) to low intensity HMV (pressure controlled ventilation). After 6 weeks, there was no statistical difference between two groups on quality of life (the COPD assessment test, WMD: 2.30, 95% CI: -2.35 to 6.95).

One retrospective observational study compared BPAP ST started in acute exacerbation of COPD (AECOPD) to BPAP ST started in stable disease and found significantly shorter survival time in the AECOPD group (median: 28.6 months vs. 52.6 months, p=0.03).

One retrospective observational study compared HMV/BPAP mix started in AECOPD to HMV/BPAP mix started in stable COPD. There were no difference on number of hospital admission for respiratory causes (changes before and after NIPPV per year: -0.6 vs. -0.3, p=0.46) and length of hospital stay for respiratory causes (changes before and after NIPPV per year: -9.8 days vs. -1.7 days, p=0.09).

One RCT compared patients treated by BPAP for 6 months to patients treated by BPAP for more than 6 months. Patients who received BPAP more than 6 months had significantly increases (43%) in the 6-minute walk distance test while the group with 6-month treatment decreased by 11% (p =0.04). No significant difference was found on quality of life (the Saint George’s Respiratory Questionnaire) between the two groups.

Comparative effectiveness evidence with SOE rating for major outcomes is summarized in Table 6. Other outcomes are summarized in Table 7. Forest plots are available in in Appendix Table H.1.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Conclusion</th>
<th>Study Design (sample size)</th>
<th>Rationale for Strength of Evidence (SOE)</th>
<th>Overall Evidence Strength (Direction of Effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMV vs. no device</td>
<td>Mortality</td>
<td>OR*:0.56; 95% CI: 0.29 to 1.08, ( \chi^2=84.3% )</td>
<td>2 Observational studies(^{16,18})</td>
<td>Risk of bias, heterogeneity and severe imprecision</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Number of hospital admissions</td>
<td>Rate Ratio: 0.50; 95% CI: 0.35 to 0.71; ( \chi^2=N/A )</td>
<td>1 Observational study (93 patients) (^{16})</td>
<td>SOE is determined based on study design; no other factors modify SOE</td>
<td>Low (reduction with HMV)</td>
<td></td>
</tr>
<tr>
<td>Comparison</td>
<td>Outcome</td>
<td>Conclusion</td>
<td>Study Design (sample size)</td>
<td>Rationale for Strength of Evidence (SOE)</td>
<td>Overall Evidence Strength (Direction of Effect)</td>
</tr>
<tr>
<td>------------------------------------</td>
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</tr>
<tr>
<td>HMV vs. CPAP</td>
<td>Number of patients with hospitalization</td>
<td>Significantly less in HMV than CPAP (p&lt;0.001)</td>
<td>1 Observational study&lt;sup&gt;45&lt;/sup&gt;</td>
<td>SOE is determined based on study design; no other factors modify SOE</td>
<td>Low (reduction with HMV)</td>
</tr>
<tr>
<td>HMV vs. BPAP</td>
<td>Number of patients with hospitalization</td>
<td>Significantly less in HMV than BPAP (p&lt;0.001)</td>
<td>1 Observational study&lt;sup&gt;45&lt;/sup&gt;</td>
<td>SOE is determined based on study design; no other factors modify SOE</td>
<td>Low (reduction with HMV)</td>
</tr>
<tr>
<td>BPAP volume assured pressure support ventilation vs. BPAP ST</td>
<td>Mortality</td>
<td>OR: 0.47; 95% CI: 0.04 to 5.69; p=0.56</td>
<td>1 RCT&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Severe imprecision</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Quality of life (Saint George’s Respiratory Questionnaire, higher score represents worse outcome)</td>
<td>WMD: -4.700; 95% Cl: -15.97 to 6.57; I²=N/A</td>
<td>1 RCT&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Severe imprecision</td>
<td>Insufficient</td>
</tr>
<tr>
<td>HMV (pressure controlled ventilation) vs. HMV (pressure support ventilation)</td>
<td>quality of life (Severe Respiratory Insufficiency Questionnaire Summary Score, higher score represents better outcome)</td>
<td>WMD: -0.14, 95% Cl: -4.90 to 4.60; I²=N/A</td>
<td>1 RCT&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Severe imprecision</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

AECOPD: acute exacerbation of chronic obstructive pulmonary disease, BPAP: bi-level positive airway pressure, CI: confidence interval, COPD: chronic obstructive pulmonary disease, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, N/A: not applicable, NOS: not otherwise specified, OR: odds ratio, RCT: randomized controlled trial, ST: spontaneous/timed mode, WMD: weighted mean difference

*: Pooled effect size from meta-analysis

**Table 7. Other effectiveness outcomes (HMV, BPAP and CPAP in COPD patients)**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Conclusion</th>
<th>Study Design (sample size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMV vs. CPAP</td>
<td>Number of patients with COPD related hospitalization</td>
<td>Significantly less in HMV than CPAP (p=0.01)</td>
<td>1 Observational study&lt;sup&gt;45&lt;/sup&gt;</td>
</tr>
<tr>
<td>BPAP vs. CPAP</td>
<td>Number of patients with exacerbations</td>
<td>OR: 0.38, 95% CI: 0.12 to 1.22; p=0.10</td>
<td>1 RCT&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td>BPAP volume assured pressure support</td>
<td>Length of hospital stay (days)</td>
<td>-1.9 days, p=0.02</td>
<td>1 RCT&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Shuttle Walk Test</td>
<td>WMD: -4.00 meters; 95% CI: -54.24 to 46.24; I²=N/A</td>
<td>1 RCT&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
<tr>
<td>Comparison</td>
<td>Outcome</td>
<td>Conclusion</td>
<td>Study Design (sample size)</td>
</tr>
<tr>
<td>------------</td>
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<td>----------------------------</td>
</tr>
<tr>
<td>ventilation vs. BPAP ST</td>
<td>Sleep quality (Epworth Sleepiness Scale, higher score represents worse outcome)</td>
<td>WMD: -2.700; 95% CI: -6.07 to 0.67; $I^2$=N/A</td>
<td>1 RCT13</td>
</tr>
<tr>
<td></td>
<td>Dyspnea (Medical research council scale, higher score represents worse outcome)</td>
<td>WMD: -0.700; 95% CI: -1.60 to 0.20; $I^2$=N/A</td>
<td>1 RCT13</td>
</tr>
<tr>
<td>HMV (pressure controlled ventilation) vs. HMV (pressure support ventilation)</td>
<td>6-minute walk distance test (meters)</td>
<td>WMD: 14; 95% CI: -42 to 70; $I^2$=N/A</td>
<td>1 RCT11</td>
</tr>
<tr>
<td>BPAP ST started in AECOPD vs. BPAP ST started in stable COPD</td>
<td>Survival time</td>
<td>28.6 months vs. 52.6 months, p=0.03</td>
<td>1 Observational study21</td>
</tr>
<tr>
<td>BPAP NOS for 6 months vs. BPAP NOS for more than 6 months</td>
<td>6-minute walk distance test</td>
<td>43% increase vs. 11 decrease, p=0.04</td>
<td>1 RCT44</td>
</tr>
<tr>
<td></td>
<td>Quality of life (Saint George’s Respiratory Questionnaire)</td>
<td>57 vs. 53, p=0.80</td>
<td>1 RCT44</td>
</tr>
<tr>
<td>HMV/BPAP mix started in AECOPD vs. HMV/BPAP mix started in stable disease</td>
<td>Number of hospital admission for respiratory causes (changes before and after the intervention)</td>
<td>-0.6 vs. -0.3, p=0.46</td>
<td>1 Observational study48</td>
</tr>
<tr>
<td></td>
<td>Length of hospital stay for respiratory causes (days per year, changes before and after the intervention)</td>
<td>-9.8 vs. -1.7, p=0.09</td>
<td>1 Observational study48</td>
</tr>
<tr>
<td>HMV/BPAP mix (pressure controlled ventilation) (high intensity) vs. HMV/BPAP mix (pressure support ventilation) (low intensity)</td>
<td>Quality of life (the COPD assessment test, higher score represents worse outcome)</td>
<td>WMD: 2.30, 95% CI: -2.35 to 6.95, $I^2$=N/A</td>
<td>1 RCT46</td>
</tr>
</tbody>
</table>

AECOPD: acute exacerbation of chronic obstructive pulmonary disease, BPAP: bi-level positive airway pressure, CI: confidence interval, COPD: chronic obstructive pulmonary disease, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, N/A: not applicable, NOS: not otherwise specified, OR: odds ratio, RCT: randomized controlled trial, ST: spontaneous/timed mode, WMD: weighted mean difference

*: Pooled effect size from meta-analysis
We conducted subgroup analyses between stable and recent exacerbation in studies comparing BPAP to no device (Table 8). In patients with stable COPD, BPAP was associated with significantly lower mortality, higher activities of daily living, and reduced dyspnea. In patients with recent exacerbation, BPAP was associated with significantly reduced need for intubation. More improvement in dyspnea were found in patients with stable COPD (p=0.005). There was no other significant difference between stable COPD and recent exacerbation.

Table 8. Subgroup analysis of studies in patients with stable COPD vs. patients with a recent exacerbation in studies comparing BPAP to no device

<table>
<thead>
<tr>
<th>Outcome</th>
<th>COPD</th>
<th>Conclusion</th>
<th>Interaction p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Stable</td>
<td>OR: 0.62; 95% CI: 0.42 to 0.92</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>Recent exacerbation</td>
<td>OR: 0.71; 95% CI: 0.47 to 1.08</td>
<td></td>
</tr>
<tr>
<td>Need for intubation</td>
<td>Stable</td>
<td>OR: 0.43; 95% CI: 0.08 to 2.46</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>Recent exacerbation</td>
<td>OR: 0.31; 95% CI: 0.11 to 0.89</td>
<td></td>
</tr>
<tr>
<td>Number of exacerbations</td>
<td>Stable</td>
<td>Rate ratio: 0.96; 95% CI: 0.81 to 1.14</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>Unstable</td>
<td>Rate Ratio: 1.00; 95% CI: 0.76 to 1.32</td>
<td></td>
</tr>
<tr>
<td>Number of hospital admissions</td>
<td>Stable</td>
<td>Rate Ratio: 0.86; 95% CI: 0.68 to 1.09</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>Unstable</td>
<td>Rate Ratio: 0.88; 95% CI: 0.44 to 1.77</td>
<td></td>
</tr>
<tr>
<td>Number of ICU admissions</td>
<td>Stable</td>
<td>Rate Ratio: 0.52; 95% CI: 0.18 1.53</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>Unstable</td>
<td>Rate Ratio: 0.29; 95% CI: 0.06 to 1.39</td>
<td></td>
</tr>
<tr>
<td>Activities of daily living (ADL) (higher score represents better outcome)</td>
<td>Stable</td>
<td>SMD: 0.22; 95% CI: 0.00 to 0.44</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Unstable</td>
<td>SMD: -0.02; 95% CI: -0.16 to 0.12</td>
<td></td>
</tr>
<tr>
<td>Quality of life (higher score represents better outcome)</td>
<td>Stable</td>
<td>SMD: 0.20; 95% CI: -0.08 to 0.49</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>Unstable</td>
<td>SMD: 0.03; 95% CI: -0.08 to 0.14</td>
<td></td>
</tr>
<tr>
<td>Dyspnea (higher score represents better outcome)</td>
<td>Stable</td>
<td>SMD: 0.33; 95% CI: 0.15 to 0.50</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Unstable</td>
<td>SMD: 0.01; 95% CI: -0.13 to 0.15</td>
<td></td>
</tr>
<tr>
<td>6-minute walk distance test</td>
<td>Stable</td>
<td>WMD: 21.45; 95% CI: -17.32 to 60.21</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>Unstable</td>
<td>WMD: 57.00; 95% CI: -93.03 to 207.03</td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval, COPD: chronic obstructive pulmonary disease, ICU: intensive care unit, OR: odds ratio, SMD: standardized mean difference, WMD: weighted mean difference

KQ3. What are the equipment parameters that are used?  

a) What are the parameters of ventilator usage (e.g. mode as determined by trigger, control and cycling variables)? 

b) What are the equipment parameters that are necessary to achieve desired outcomes (e.g. flow capabilities, settings, etc.)?  

c) What are the parameters of prescribed patient usage (e.g. frequency of use, duration of use throughout the day, etc.)?  

d) In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?

Key Points-KQ3

- For BPAP devices, the modes utilized were BPAP S, BPAP ST, BPAP volume assured pressure support ventilation, and pressure controlled ventilation.
- For HMV devices, the modes utilized were pressure support ventilation and pressure controlled ventilation.
• For CPAP devices, modes were not specified.
• Prescribed device usage per day varied from ≥5-12 hours. Actual mean device usage per day ranged from 4.5-9.0 hours.

Twenty-eight studies evaluated patients who used BPAP devices.15, 17, 18, 30, 34, 37, 43-45 6, 15, 16, 19-29, 32, 33, 35, 36, 40-42 Seventeen studies evaluated patients who used BPAP ST. 6, 15, 16, 19-22, 25-29, 33, 35, 36, 40, 42 BPAP ST equipment parameters included IPAP, EPAP, and a spontaneous/timed (ST) breathing mode with a backup respiratory rate. Three studies evaluated patients who used BPAP S.23, 24, 32 BPAP S equipment parameters included IPAP, EPAP and a spontaneous (S) mode without a backup respiratory rate. One study evaluated patients who used BPAP volume assured pressure support ventilation.15 Volume assured pressure support ventilation equipment parameters included IPAP, EPAP, and a target minute ventilation. Two studies evaluated patients who used BPAP pressure controlled ventilation.34, 43 BPAP pressure controlled ventilation equipment parameters included IPAP, EPAP, backup respiratory rate, and inspiratory time. Six studies evaluated patients who used BPAP NOS (unclear which mode).17, 18, 30, 37, 44, 45 Four studies evaluated patients who used HMV devices in the pressure support ventilation and pressure controlled ventilation modes.31, 34, 43, 47 Pressure support equipment parameters included inspiratory pressure, PEEP, inspiratory flow trigger and expiratory flow trigger. Pressure controlled ventilation parameters included inspiratory pressure, PEEP, inspiratory time, and respiratory rate. One study did not specify the mode of HMV.45 Two studies evaluated patients who used a mixture of bilevel BPAP and HMV devices.46, 48. Two studies evaluated patients who used CPAP devices.18, 22 CPAP equipment parameters included CPAP.

Twenty-five studies reported the model and manufacturer of the device used.6, 15, 16, 18-21, 23-28, 30-35, 37, 39-41, 46-48 One study reported the manufacturer of the device used only.29

The prescribed daily device use of included studies was ≥5 hours,30, 33 ≥6 hours,6, 18, 29 >8 hours,22, 24 and >12 hours.47 Actual daily device usage ranged from mean of 4.5-9.0 hours/day. Actual mean recorded IPAP ranged from 12.0-31.6 cmH2O. Actual mean recorded EPAP ranged from 3.9-6.0 cmH2O. Actual respiratory rates ranged from 8.0-20.7 breaths/minute.

KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g. patient education, ongoing smoking cessation, respiratory therapist led home care)?

**Key Points-KQ4**

- Evidence is lacking to determine the effect of specific respiratory home services on outcomes.
- Respiratory services provided in the home included: telephone hotline staffed by nurses, scheduled phone calls by respiratory therapists, home visits by respiratory therapists, smoking cessation, and a comprehensive home care program with evaluation and treatment of physical, occupational, and dietary needs.
Fourteen studies\textsuperscript{6, 15, 18, 21, 22, 24, 26, 29, 32, 35, 48, 75} described respiratory services provided in the home. These services included a telephone hotline staffed by healthcare professionals including nurses, respiratory therapists, and/or others,\textsuperscript{15, 21, 22, 29, 32, 75} scheduled phone calls by nurses, respiratory therapists and/or others,\textsuperscript{18, 24, 26, 35} home visits by nurses, respiratory therapists, and/or others,\textsuperscript{18} and smoking cessation services NOS.\textsuperscript{6, 48} One study described provision of a home care program that included initial evaluation of physical, occupational, and dietary needs; monthly physician visits; monthly education about treatments and correct medication use and coping strategies; periodic phone calls.\textsuperscript{26}

KQ5. What are the professional guidelines and statements which address KQ 1 to KQ 4?

Information related to clinical guidelines can be found in Appendix Table G.2.
Thoracic Restrictive Diseases

Seven42, 43, 49-53 studies with a total of 202 patients were included. The characteristics of the studies are listed in appendix Table D.1. Five evaluated HMV,34, 43, 51-53 three BPAP, 42, 49, 50 and zero CPAP. These studies were conducted in the United States (n=0), Canada (n=0), Europe (n=6), and other countries (n=1). We also identified six clinical practice guidelines relevant to KQ1-4(Appendix).76, 77, 83, 85, 86, 92

Overall risk of bias of the included studies was rated as moderate due to unclear conflict of interest (62.5%) and inadequate followup (37.5%) in the observational studies (Appendix Tables E.1 and E.2.).

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bilevel Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface.

Key Points-KQ1

- The criteria used to start NIPPV were variable and most commonly included: PaCO2 >45mmHg, FVC<40% or MIP <60cmH2O or nocturnal SaO2 < 88% for ≥ 5 consecutive minutes.
- All studies enrolled patients with stable disease (not in acute respiratory failure).
- No studies compared the initiation criteria between different devices or evaluated criteria for device continuation.
- Processes used to titrate NIPPV were variable and used the following targets: reduction in hypercapnia, reduction in hypoxia, achievement of target tidal volumes, and reduction in patient symptoms.

Seven studies42, 43, 49-53 described criteria for initiation of HMV, BPAP, and/or CPAP devices in patients with TRD. Five studies42, 49-52 evaluated patients who had not yet started home device use and two studies43, 53 evaluated patients with established home device use.

No studies directly evaluated differences between the criteria to start different devices (HMV vs. BPAP vs. CPAP). Indirectly, the criteria used to start each device were not different.

The following patient and laboratory criteria were used to start home NIPPV using a HMV, BPAP, and or CPAP device:
**Included Diseases**

Studies enrolled patients with the following diagnoses: kyphoscoliosis, fibrothorax, thoracoplasty, or post-tuberculosis sequelae. Only one study defined the definition of kyphoscoliosis by Cobb scoliosis angle >90 degrees.\(^51\)

**PaCO2**

Four studies included patients with hypercapnia: PaCO2 >45mmHg,\(^49,50,52\) and >47mmHg.\(^51\)

**Stable disease versus recent exacerbation**

Four studies enrolled patients with stable disease (no infection in past 3 months, stable PaCO2 for past 3 months, no hospital admission in past 1 month, absence of severe acidosis)\(^49-52\) (563,593,1723,30000), and 3 studies did not comment on stability of disease.\(^42,43,53\)

**Others**

Two studies also included patients with FVC<40% or MIP <60cmH2O, or nocturnal SaO2 < 88% for ≥ 5 consecutive minutes.\(^49,50\)

**Targets of device titration**

Most studies reported using maximum tolerated respiratory pressures (such as IPAP and/or EPAP) needed to achieve the following stated goals: “desired tidal volume” NOS,\(^42\) normal PaCO2 or a reduction in baseline PaCO2 by ≥10mmHg,\(^49\) maximum change in blood gasses NOS,\(^50\) and maximum reduction in PaCO2 as well as optimal patient tolerance, lowest air leakage, and nocturnal SaO2>90%.\(^51\)

**Device continuation**

No studies described criteria for device continuation.

KQ2. What is the effect of HMV, a BPAP, or a CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

**Key Points-KQ2**

- HMV (compared with no device) was associated with lower mortality (SOE: low).
- No studies compared outcomes between HMV and BPAP devices.

One observational study of 33 patients with kyphoscoliosis and chronic respiratory insufficiency compared HMV plus long-term oxygen therapy to long-term oxygen therapy.\(^53\) With a followup from 1 year to 11 years, patients treated with HMV plus long-term oxygen were found to have significantly lower mortality than those treated with long-term oxygen alone (OR=0.13, 95% CI: 0.03 to 0.67).
In another observational study, ten stable patients with mild-to-moderate chronic respiratory failure (PaCO2 between 45 mm Hg and 55 mm Hg) were treated with HMV at night for 3 months. These patients were compared with ten matching patients who received standard care without HMV. Patients with HMV were found to have significantly better improvements in inspiratory threshold loading test (WMD: 450.00; 95% CI: 273.17 to 626.83), cycle ergometer test (WMD: 240.0; p<0.001), and shuttle walking test (WMD: 100.00; p<0.001) than patients with standard care. Comparative effectiveness evidence with SOE rating for major outcomes is summarized in Table 9. Other outcomes are summarized in Table 10.

<table>
<thead>
<tr>
<th>Table 9. Major effectiveness outcomes with SOE (HMV vs. no device in patients with thoracic restrictive diseases)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Mortality</td>
</tr>
</tbody>
</table>

CI: confidence interval, HMV: home mechanical ventilation, N/A: not applicable, OR: odds ratio, WMD: weighted mean difference

<table>
<thead>
<tr>
<th>Table 10. Other effectiveness outcomes (HMV vs. no device in patients with thoracic restrictive diseases)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Physical activity (Inspiratory Threshold Loading test, endurance time)</td>
</tr>
<tr>
<td>Physical activity (Cycle Ergometry Test, endurance time)</td>
</tr>
<tr>
<td>Physical activity (Inspiratory Threshold Loading test, endurance time)</td>
</tr>
</tbody>
</table>

CI: confidence interval, HMV: home mechanical ventilation, N/A: not applicable, OR: odds ratio, WMD: weighted mean difference
KQ3. What are the equipment parameters that are used?  a) What are the parameters of ventilator usage (e.g. mode as determined by trigger, control and cycling variables)?  b) What are the equipment parameters that are necessary to achieve desired outcomes (e.g. flow capabilities, settings, etc.)?  c) What are the parameters of prescribed patient usage (e.g. frequency of use, duration of use throughout the day, other)?  d) In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?

Key Points-KQ3

- For BPAP devices, the modes utilized were BPAP ST and BPAP NOS (unclear which mode)
- For HMV devices, the modes utilized were pressure controlled ventilation, volume assist controlled ventilation, and volume/pressure cycled NOS.
- Prescribed usage included ≥ 7 hours/day. Actual mean device usage per day ranged from 6.0-7.3 hours.

Three studies evaluated patients who used BPAP devices.\textsuperscript{42, 49, 50} One study evaluated patients who used BPAP ST.\textsuperscript{42} BPAP ST equipment parameters included IPAP, EPAP, and a spontaneous/timed (ST) breathing mode with a backup respiratory rate. No studies evaluated patients who used BPAP S. Two studies evaluated patients who used BPAP NOS (unclear if ST or S mode).\textsuperscript{49, 50} No studies evaluated patients who used volume assured pressure support (VAPS) ventilation. Five studies evaluated patients who used HMV devices.\textsuperscript{34, 43, 51-53} HMV equipment parameters used were pressure controlled ventilation,\textsuperscript{34, 43} volume assist control ventilation,\textsuperscript{52} and volume/pressure cycled NOS.\textsuperscript{51, 53} No studies evaluated patients who used CPAP devices.

Five studies reported the model and manufacturer of the device used.\textsuperscript{49-53} Two studies did not report the model or manufacturer of the device used.\textsuperscript{42, 43}

The prescribed daily device use of included studies was ≥ 7 hours daily.\textsuperscript{49} Actual device usage ranged from mean of 6.0-7.3 hours/day. Actual mean recorded IPAP ranged from 20.9-22.0 cmH2O. Actual mean recorded EPAP ranged from 4.2-5.3 cmH2O. One study reported actual respiratory rates of mean 19.1 breaths/minute.

KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g. patient education, ongoing smoking cessation, respiratory therapist led home care)?
Key Points-KQ4

- Evidence is lacking to determine the effect of specific respiratory home services on outcomes.
- Respiratory services provided in the home included: telephone hotline

One study described respiratory services provided in the home which included a telephone hotline staffed by healthcare professionals including nurses, respiratory therapists, and/or others.49

KQ5. What are the professional guidelines and statements which address KQ 1 to KQ 4?

Information related to clinical guidelines can be found in Appendix Table G.4.

Neuromuscular Disease (NMD)

Thirteen studies49, 50, 54-64 with a total of 1,015 patients were included. The characteristics of the studies are listed in Appendix Table D.1. Four evaluated HMV,55, 57, 62, 63 eleven BPAP,49, 50, 54, 56-61, 63, 64 and zero CPAP. These studies were conducted in the United States (n=0), Canada (n=0), Europe (n=12), and other countries (n=1). We also identified ten clinical practice guidelines relevant to KQ1-4(Appendix Table G.3.).76, 77, 83, 85, 86, 89-93

Overall risk of bias was rated as moderate to high due to unable to blind patients, providers, or outcome assessors, unclear risk of allocation concealment and outcome reporting in the RCT and unknown conflict of interest and high risk of outcome assessment in observational studies (Appendix Tables E.1. and E.2.).

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bilevel Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface.

Key Points-KQ1

- The criteria used to start NIPPV were variable and most commonly included: PaCO2 >45mmHg) or FVC<50% or MIP <60cmH2O, or nocturnal SaO2 < 88% for ≥ 5 consecutive minutes.
- No studies compared the initiation criteria between different devices or evaluated criteria for device continuation.
- Processes used to titrate NIPPV were variable and used the following targets: reduction in hypercapnia, reduction in hypoxia, and reduction in patient symptoms.
Thirteen studies\textsuperscript{49, 50, 54-60, 62-64} described criteria for initiation and/or continuation of HMV, BPAP, and/or CPAP devices in patients with NMD. Eleven studies\textsuperscript{49, 50, 55-60, 62-64} evaluated patients who had not yet started home device use and two studies\textsuperscript{50, 54} evaluated patients with established home device use.

No studies directly evaluated differences between the criteria to start different devices (HMV vs. BPAP vs. CPAP). Indirectly, the criteria used to start each device were not different.

The following patient and laboratory criteria were used to start home NIPPV using a HMV, BPAP, and or CPAP device:

**Included Diseases**

Studies enrolled patients with the following diagnoses: ALS (based on El Escorial criteria or not otherwise specified)\textsuperscript{54-64} and NMD not otherwise specified.\textsuperscript{49, 50}

**Other characteristics**

Five studies enrolled patients with the following characteristics PaCO\textsubscript{2}>45mmHg or FVC<50\% or MIP<60cmH\textsubscript{2}O, or nocturnal SaO\textsubscript{2}<88\% for ≥ 5 consecutive minutes.\textsuperscript{49, 50, 57-59} One study enrolled patients with PaCO\textsubscript{2}>45mmHg and FVC<50\% and nocturnal SaO\textsubscript{2}<90\% for ≥ 5\% of time.\textsuperscript{62} One study enrolled patients with PaCO\textsubscript{2}>45mmHg or FVC<70\% or MIP<70\% or subjective respiratory discomfort or 20\% decline in MIP or FVC over 3 months.\textsuperscript{64} One study enrolled patients with orthopnea with Pimax<60\% or “symptomatic daytime hypercapnia.”\textsuperscript{60}

**Targets of device titration**

Most studies reported using maximum tolerated respiratory pressures (such as IPAP and/or EPAP) needed to achieve the following stated goals: normalization of blood gasses, symptom relief, elimination of hypoxia (daytime and nocturnal).

**Device continuation**

No studies described criteria for device continuation.

KQ2. What is the effect of HMV, a BPAP, or a CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

**Key Points-KQ2**

- BPAP (compared with no device) was associated with lower mortality (SOE: low), better quality of life (SOE: low).
Three studies (1 RCT\(^60\) and 2 Observational studies\(^{56,58}\)) compared BPAP to no device. BPAP was associated with significantly lower mortality than no device (OR=0.04, 95% CI: 0.00 to 0.34, low SOE). Patients with BPAP were also found to have better median survival length (219 days vs. 171 days, \(p=0.01\)) and quality of life measured by SF-36 mental components (168 vs. 99, \(p<0.01\)) and physical component (150 vs. 81, \(p<0.01\)).

One observational study of 140 ALS patients compared HMV (volume assist control ventilation) to no device.\(^62\) The HMV group was found to have significantly longer survival time than the group not treated with any device (mean: 18.50 months vs. 3.00 months, \(p=0.001\)). The significant difference was also found in patients with no or moderate bulbar dysfunction (mean: 20.00 months vs. 3.00 months, \(p=0.0001\)) and in patients with severe bulbar dysfunction (mean: 13.00 months vs. 3.00 months, \(p=0.001\)).

One observational study of 144 ALS patients compared HMV (volume cycled) to BPAP (pressure cycled) and found no significant difference on length of survival (median 15.00 months vs. median 15.00 months, \(p=0.53\)).\(^{57}\)

One RCT compared BPAP outpatient initiation to BPAP inpatient initiation in 50 ALS patients.\(^{64}\) After 3-month follow up, the group with outpatient initiation was not significantly different from the group with inpatient initiation on dyspnea and sleep quality.

One observational study evaluated BPAP patients who were “correctly ventilated” to those “insufficiently ventilated” patients.\(^{54}\) The “correctly ventilated” patients had significantly higher survival than those “insufficiently ventilated” patients (OR= 0.25; 95% CI: 0.10 to 0.64).

One prospective observational study evaluated the daily use of BPAP in ALS patients.\(^{59}\) The group with >=4 hours/days use had significantly longer survival time from BPAP start to death (median: 18 months (interquartile range: 7 to 28) vs. 6 months (interquartile range: 3 to 12), \(p<0.001\)).

One observational study compared HMV started after outpatient pulmonary evaluation to HMV started in an emergency situation in hospital.\(^{55}\) Patients started HMV after outpatient pulmonary evaluation had significantly longer length of survival than those started in an emergency setting (mean survival: 12.3 months vs. 2.8 months, \(p<0.004\)).

One observational study compared HMV/BPAP mix started early with FVC>=80% to HMV/BPAP mix started late with FVC<80%.\(^{63}\) The patients started early were found to have significantly longer survival time (31.33 months vs. 27.51 months, \(p=0.01\)) and lower mortality (HR: 0.46, 95% CI: 0.29 to 0.74; \(p=0.001\)) than the patients started late.

Comparative effectiveness evidence with SOE rating for major outcomes is summarized in Table 11. Other outcomes are summarized in Table 12. Forest plots are available in in Appendix Table H.2.
Table 11. Major effectiveness outcomes with SOE (all devices in patients with neuromuscular disease)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Conclusion</th>
<th>Study Design (sample size)</th>
<th>Rationale for Strength of Evidence (SOE)</th>
<th>Overall Evidence Strength (Direction of Effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAP vs. No Device</td>
<td>Mortality</td>
<td>OR*: 0.04; 95% CI: 0.00 to 0.34; I²=0.0% 334 fewer per 1000 patients (537 fewer to 131 fewer)</td>
<td>2 Observational studies (73 patients) 56, 58</td>
<td>SOE is determined based on study design; no other factors modify SOE</td>
<td>Low (reduction with BPAP)</td>
</tr>
<tr>
<td></td>
<td>Quality of life (SF-36 physical component, (higher score represents better outcome))</td>
<td>WMD:69; p=0.01; I²=N/A</td>
<td>1 RCT(41 patients) 56</td>
<td>Severe imprecision (single study with a small number of patient)</td>
<td>Low (increased QoL scores with BPAP)</td>
</tr>
</tbody>
</table>

BPAP: bi-level positive airway pressure, CI: confidence interval, HMV: home mechanical ventilation, N/A: not applicable, OR: odds ratio, RCT: randomized controlled trial, SF-36: Medical Outcomes Study Questionnaire Short Form, ST: spontaneous/timed mode, WMD: weighted mean difference

*: Pooled effect size from meta-analysis
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Conclusion</th>
<th>Study Design (sample size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAP vs. No Device</td>
<td>Length of survival Dyspnea, (Chronic Respiratory Disease Questionnaire, dyspnea, higher score represents better outcome)</td>
<td>Median 219 days vs. 171 days; p=0.01 WMD:147; p&lt;0.001; I²=N/A</td>
<td>1 RCT(41 patients)80</td>
</tr>
<tr>
<td>HMV vs. BPAP</td>
<td>Length of survival</td>
<td>Median:15.00 months vs. 15.00 months; p=0.53</td>
<td>1 Observational study (144 patients)77</td>
</tr>
<tr>
<td>HMV vs. No Devices</td>
<td>Length of survival</td>
<td>Mean: 18.50 months, vs. 3.00 months, p=0.001</td>
<td>1 Observational study (140 patients)62</td>
</tr>
<tr>
<td>BPAP “correctly ventilated” vs. BPAP “insufficiently ventilated”</td>
<td>Mortality</td>
<td>OR:0.25; 95% CI: 0.10 to 0.64; I²=N/A</td>
<td>1 Observational study (82 patients)54</td>
</tr>
<tr>
<td>BPAP &gt;=4 hours daily vs. &lt;4 hours daily</td>
<td>Length of survival</td>
<td>Median: 18 months (interquartile range: 7 to 28) vs. 6 months (interquartile range: 3 to 12); p=0.001</td>
<td>1 Observational study (71 patients)69</td>
</tr>
<tr>
<td>BPAP volume assured pressure support ventilation outpatient initiation vs. BPAP volume assured pressure support ventilation inpatient initiation</td>
<td>Dyspnea (measured by VAS score, (higher score represents worse outcome))</td>
<td>Daily dyspnea: WMD: -0.37, p=0.19 Night dyspnea: WMD: 0.03, p=0.97</td>
<td>1 RCT (50 patients)64</td>
</tr>
<tr>
<td></td>
<td>Sleep quality (measured by VAS score, (higher score represents better outcome))</td>
<td>WMD: -1.57, p=0.12</td>
<td>1 RCT (50 patients)64</td>
</tr>
<tr>
<td>HMV/BPAP mix started in FVC 80% (early) vs. HMV/BPAP mix started in FVC &lt;80% (late)</td>
<td>Mortality</td>
<td>HR: 0.46, 95% CI: 0.29 to 0.74; p=0.001</td>
<td>1 Observational study (194 patients)63</td>
</tr>
<tr>
<td></td>
<td>Length of survival</td>
<td>Mean survival: 31.33 months vs. 27.51 months, p=0.01</td>
<td>1 Observational study (194 patients)63</td>
</tr>
<tr>
<td>HMV (pressure support ventilation mode or BPAP ST mode) started after outpatient pulmonary evaluation vs. HMV (pressure support ventilation mode or BPAP ST mode) started in an emergency situation without prior outpatient pulmonary evaluation</td>
<td>Length of survival</td>
<td>Mean survival: 12.3 months vs. 2.8 months; p&lt;0.004</td>
<td>1 Observational study65</td>
</tr>
</tbody>
</table>
KQ3. What are the equipment parameters that are used? a) What are the parameters of ventilator usage (e.g. mode as determined by trigger, control and cycling variables)? b) What are the equipment parameters that are necessary to achieve desired outcomes (e.g. flow capabilities, settings, etc.)? c) What are the parameters of prescribed patient usage (e.g. frequency of use, duration of use throughout the day, other)? d) In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?

Key Points-KQ3

- For BPAP devices, the modes utilized were BPAP ST, BPAP NOS (unclear if S or ST), and BPAP volume assured pressure support.
- For HMV devices, the modes utilized were pressure support, pressure control, and volume assist controlled ventilation.
- Prescribed device usage per day varied from ≥4-7 hours. Actual mean device usage per day ranged from 3.8-9.3 hours.

Ten studies evaluated patients who used BPAP devices. Four studies evaluated patients who used BPAP ST. BPAP ST equipment parameters included IPAP, EPAP, and a spontaneous/timed (ST) breathing mode with a backup respiratory rate. No studies evaluated patients who used BPAP S. One study evaluated patients who used BPAP volume assured pressure support. Four studies evaluated patients who used BPAP NOS (unclear if ST or S mode). Three studies evaluated patients who used HMV devices. HMV modes were volume assist control ventilation and pressure support ventilation. One study evaluated patients who used either BPAP or HMV devices. No studies evaluated patients who used CPAP devices.

Ten studies reported the model and manufacturer of the device used. Three studies did not report the model or manufacturer of the device used.
The prescribed daily device use of included studies ranged from ≥4-7 hours/day. Actual device usage ranged from mean of 3.8-9.3 hours/day. Actual mean recorded IPAP ranged from 12.0-15.0 cmH₂O. Actual mean recorded EPAP ranged from 4.0-5.0 cmH₂O. Actual mean respiratory rates ranged from 11-14 breaths/minute.

KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g. patient education, ongoing smoking cessation, respiratory therapist led home care)?

Key Points-KQ4

- Respiratory services provided in the home included: telephone hotline, scheduled phone calls, and cough assistance including mechanical cough assist devices provided by a respiratory therapist.
- Weekly telemonitoring was associated with significantly lower rates of office visits, ER visits, and hospital admission, with no change in mortality.

Nine studies described respiratory services provided in the home. These services included a telephone hotline staffed by healthcare professionals including nurses, respiratory therapists, and/or others, phone calls by nurses, respiratory therapists and/or others, instruction and provision of cough assistance including mechanical cough assist devices by a respiratory therapist.

One RCT evaluated the effectiveness of home telemonitoring in 40 ALS patients treated by BPAP ST. The BPAP ST + Weekly telemonitoring group had significantly lower number of office visits (IRR: 0.34, 95% CI: 0.29 to 0.38); ER visits (IRR: 0.19; 95% CI: 0.10 to 0.37); hospital admission (IRR: 0.17; 95% CI: 0.07 to 0.41). There was no significant difference on mortality (OR: 1.00; 95% CI: 0.24 to 4.18) or median survival time (from BPAP adoption to death) (865 days vs. 334 days, p=0.13).

KQ5. What are the professional guidelines and statements which address KQ 1 to KQ 4?

Information related to clinical guidelines can be found in Appendix Table G.3.
Obesity Hypoventilation Syndrome

Nine studies with a total of 577 patients were included. The characteristics of the studies are listed in Appendix Table D.1. Three evaluated HMV, eight BPAP, and three CPAP. 

These studies were conducted in the United States (n=0), Canada (n=0), Europe (n=6), and other countries (n=3). We also identified five clinical practice guidelines relevant to KQ1-4(Appendix).

Overall risk of bias was rated as moderate due to unable to blind patients or provider accessors, high risk of conflicts of interest in the RCT and selective patient population in observational studies(Appendix Table E.1. and E.2.).

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bilevel Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface?

Key Points-KQ1

- The criteria used to start NIPPV were variable but most commonly included: BMI >30kg/m2, PaCO2>45mmHg, and other causes of hypercapnia ruled out.
- No studies compared the initiation criteria among different devices or evaluated criteria for device continuation.
- Processes used to titrate NIPPV were variable and used the following targets: reduction in hypercapnia, reduction in hypoxia (including nocturnal hypoxia), achievement of target tidal volumes, and reduction in patient symptoms.

Nine studies described criteria for initiation and/or continuation of HMV, BPAP, and/or CPAP devices in patients with OHS, all of which evaluated patients who had not yet started home device use. There were no major differences in criteria used to start BPAP versus HMV.

Elevated BMI

All studies enrolled patients with elevated BMI: >30 kg/m2, >33 kg/m2, and >40kg/m2.

Hypercapnia

All studies enrolled patients with hypercapnia: PaCO2>45mmHg, >47mmHg, and >53mmHg. All studies reported that PaCO2 measurements should be performed in patients while awake and in a stable state. Some studies included normal pH as a way of ensuring stable respiratory state: pH 7.35-7.45, pH>7.35.
Other causes of hypercapnia ruled out
All studies reported including patients in whom other causes of hypercapnia/hypoventilation had been excluded such as COPD, NMD, TRD, respiratory depressant medications, narcolepsy, or severe heart failure.

Other characteristics
One study excluded patients with SaO2 <80% for 10 minutes in absence of apnea, TcCO2 during REM ≥10mmHg, increase in afternoon to morning PaCO2 ≥10mmHg in patients with awake PaCO2 >55 mmHg.70

Targets of device titration
Studies reported using maximum tolerated respiratory pressures (such as IPAP and/or EPAP) or other device changes needed to achieve the following goals:
1) Reduction in hypercapnia: maximum reduction in PaCO2,47, 51, 67 PaCO2<45mmHg,66 reduction in baseline PaCO2 ≥5mmHg.66
2) Tidal volumes or minute ventilation: desired tidal volume.65
3) Overcome “obstructive events and nocturnal hypoventilation”.65, 69
4) Patient tolerance, air leakage.47, 51
5) Absence of hypoxia: SaO2>90%.66, 67

Device continuation
No studies described criteria for device continuation.

KQ2. What is the effect of HMV, a BPAP, or a CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

Key Points-KQ2
- HMV/BPAP mix (compared no device) was no difference in quality of life (SOE: insufficient).
- HMV/BPAP mix (compared with CPAP) was no difference in quality of life (SOE: insufficient).
- CPAP (compared with no device) was no difference in quality of life (SOE: insufficient).
- BPAP (compared with CPAP) was no difference in hospital admissions (SOE: insufficient), or quality of life (SOE: insufficient).

Two RCTs of 96 OHS patients compared BPAP to CPAP.65, 70 No significant difference was found on hospital admission, sleep quality, quality of life, exercise tolerance, or withdrawals.

One RCT randomized 221 patients to CPAP (n=80), HMV/BPAP (n=71), or lifestyle modification (n=70) and follow these patients for 2-month.67 The HMV/BPAP group and the
CPAP group reported significantly better sleep quality measured by Epworth Sleepiness Scale than the lifestyle modification group (HMV/BPAP: -3.80; 95% CI: -5.36 to -2.25; CPAP: -3.30; 95% CI: -4.76 to -1.84). No significant difference between the HMV/BPAP and CPAP group. Patients treated by HMV/BPAP were found to have significant better outcomes on 6-minute walk distance tests than CPAP (26.00 meters; 95% CI: 6.70 to 45.30). There was no difference between groups on quality of life (SF-36).

One RCT of 55 patients compared BPAP to lifestyle counseling.\textsuperscript{68} No significant difference were found on sleep quality (Epworth Sleepiness Score, -1.30; 95% CI: -4.98 to 2.38, p=0.49).

One RCT randomized 50 patients with obesity hypoventilation syndrome to either BPAP volume assured pressure support ventilation or BPAP ST.\textsuperscript{69} There was no statistically significant difference on quality of life (Severe Respiratory Insufficiency Questionnaire summary score, mean difference: 5, p=0.21), or sleep quality (Epworth Sleepiness Score; 1, p=0.43)

Comparative effectiveness evidence with SOE rating for major outcomes is summarized in Table 13. Other outcomes are summarized in Table 14. Forest plots are available in in Appendix Table H.3.

**Table 13. Major effectiveness outcomes with SOE (all devices in patients with obesity hypoventilation syndrome)**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Conclusion</th>
<th>Study Design (sample size)</th>
<th>Rationale for Strength of Evidence (SOE)</th>
<th>Overall Evidence Strength (Direction of Effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAP vs. CPAP</td>
<td>Number of patients with hospital admissions</td>
<td>OR; 1.08; 95% CI: 0.35 to 5.41; I(^2)=N/A 7 more per 1000 patients (145 fewer to 159 more)</td>
<td>1 RCT (60 patients) \textsuperscript{65}</td>
<td>Severe imprecision</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Quality of life (SF-36 Physical Component, higher score represents better outcome)</td>
<td>WMD(^*): -0.89; 95% CI: -5.57 to 3.80; I(^2)=0.0%</td>
<td>2 RCTs (96 patients) \textsuperscript{65,70}</td>
<td>Risk of bias and severe imprecision</td>
<td>Insufficient</td>
</tr>
<tr>
<td>HMV/BPAP mix (all with bilevel pressure with assured volume) vs. no device</td>
<td>Quality of life (SF-36 Physical Component, higher score represents better outcome)</td>
<td>WMD: 1.60; 95% CI: -0.98 to 4.18; I(^2)=N/A</td>
<td>1 RCT (141 patients) \textsuperscript{67}</td>
<td>Severe imprecision</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Comparison</td>
<td>Outcome</td>
<td>Conclusion</td>
<td>Study Design (sample size)</td>
<td>Rationale for Strength of Evidence (SOE)</td>
<td>Overall Evidence Strength (Direction of Effect)</td>
</tr>
<tr>
<td>------------</td>
<td>---------</td>
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<td>-------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>HMV/BPAP mix (all with bilevel pressure with assured volume) vs. CPAP</td>
<td>Quality of life (SF-36 Physical Component, higher score represents better outcome)</td>
<td>WMD: 0.60; 95% CI: -2.21 to 3.41; I²=N/A</td>
<td>1 RCT(151 patients)</td>
<td>Severe imprecision</td>
<td>Insufficient</td>
</tr>
<tr>
<td>CPAP vs. no device</td>
<td>Quality of life (SF-36 Physical Component, higher score represents better outcome)</td>
<td>WMD: 1.00; 95% CI: -1.52 to 3.52; I²=N/A</td>
<td>1 RCT(150 patients)</td>
<td>Severe imprecision</td>
<td>Insufficient</td>
</tr>
<tr>
<td>BPAP volume assured pressure support ventilation vs. BPAP ST</td>
<td>Quality of life (Severe Respiratory Insufficiency Questionnaire summary score, higher score represents better outcome)</td>
<td>Mean: 5, p=0.21</td>
<td>1 RCT(50 patients)</td>
<td>Severe imprecision</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

BPAP: bi-level positive airway pressure, CI: confidence interval, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, N/A: not applicable, OR: odds ratio, RCT: randomized controlled trial, SF-36: Medical Outcomes Study Questionnaire Short Form, ST: spontaneous/timed mode, WMD: weighted mean difference

*: Pooled effect size from meta-analysis

Table 14. Other effectiveness outcomes (all devices in patients with obesity hypoventilation syndrome)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Conclusion</th>
<th>Study Design (sample size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAP vs. CPAP</td>
<td>Sleep Quality (Epworth Sleepiness Scale, higher score represents worse outcome)</td>
<td>WMD*: 0.35; 95% CI: -2.23 to 2.29; I²=0.0%</td>
<td>2 RCTs (96 patients)</td>
</tr>
<tr>
<td>HMV/BPAP mix (all with bilevel pressure with assured volume) vs. no device</td>
<td>6-minute walk distance test (meters)</td>
<td>WMD: 16.00; 95% CI: -4.70 to 36.70; I²=N/A</td>
<td>1 RCT (141 patients)</td>
</tr>
<tr>
<td></td>
<td>Sleep Quality (Epworth Sleepiness Scale, higher score represents worse outcome)</td>
<td>WMD: -3.80; 95% CI: -5.36 to -2.25; I²=N/A</td>
<td>1 RCT(141 patients)</td>
</tr>
</tbody>
</table>
### Comparison

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Conclusion</th>
<th>Study Design (sample size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMV/BPAP mix (all with bilevel pressure with assured volume) vs. CPAP</td>
<td>Physical activity (6-minute walk distance test, meters)</td>
<td>WMD: 26.00; 95% CI: 6.70 to 45.30; I²=N/A</td>
<td>1 RCT (151 patients) ⁶⁷</td>
</tr>
<tr>
<td></td>
<td>Sleep Quality (Epworth Sleepiness Scale, higher score represents worse outcome)</td>
<td>WMD: -0.50; 95% CI: -2.05 to 1.05; I²=N/A</td>
<td>1 RCT (151 patients) ⁶⁷</td>
</tr>
<tr>
<td>CPAP vs. no device</td>
<td>Quality of life (SF-36 Physical Component, higher score represents better outcome)</td>
<td>WMD: 1.00; 95% CI: -1.52 to 3.52; I²=N/A</td>
<td>1 RCT (150 patients) ⁶⁷</td>
</tr>
<tr>
<td>BPAP vs. no device</td>
<td>Sleep Quality (Epworth Sleepiness Scale, higher score represents worse outcome)</td>
<td>WMD: -1.30; 95% CI: -4.98 to 2.38; I²=N/A</td>
<td>1 RCT (37 patients) ⁶⁸</td>
</tr>
<tr>
<td>BPAP volume assured pressure support ventilation vs. BPAP ST</td>
<td>Sleep quality (Epworth Sleepiness Score, higher score represents worse outcome)</td>
<td>Mean: 1, p=0.43</td>
<td>1 RCT (50 patients) ⁹⁹</td>
</tr>
</tbody>
</table>

BPAP: bi-level positive airway pressure, CI: confidence interval, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, N/A: not applicable, OR: odds ratio, RCT: randomized controlled trial, SF-36: Medical Outcomes Study Questionnaire Short Form, ST: spontaneous/timed mode, WMD: weighted mean difference

*: Pooled effect size from meta-analysis

### KQ3. What are the equipment parameters that are used?

a) What are the parameters of ventilator usage (e.g. mode as determined by trigger, control and cycling variables)?

b) What are the equipment parameters that are necessary to achieve desired outcomes (e.g. flow capabilities, settings, etc.)?

c) What are the parameters of prescribed patient usage (e.g. frequency of use, duration of use throughout the day, other)?

d) In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?

### Key Points-KQ3

- For BPAP devices, the modes utilized were BPAP ST, BPAP S, and BPAP NOS (unclear if S or ST)
- For HMV devices, the modes utilized were volume/pressure cycled NOS, pressure support and pressured controlled ventilation as well as a mixture of bilevel BPAP/HMV each with assured volume modes.
Six studies\textsuperscript{42, 65, 66, 68,70} evaluated patients who used BPAP devices. Five studies\textsuperscript{42, 65, 66, 68, 69} evaluated patients who used BPAP ST. BPAP ST equipment parameters included IPAP, EPAP, and a spontaneous/timed (ST) breathing mode with a backup respiratory rate. One study evaluated patients who used BPAP S.\textsuperscript{70} BPAP S equipment parameters included IPAP, EPAP and a spontaneous (S) mode without a backup respiratory rate. One study evaluated patients who used volume assured pressure support (VAPS) ventilation.\textsuperscript{69} Volume assured pressure support ventilation equipment parameters included IPAP, EPAP, and a target minute ventilation. One study evaluated patients who used a mixture of bilevel BPAP and HMV devices each with with assured volume modes.\textsuperscript{67} One study evaluated patients who used HMV devices with a combination of volume or pressure cycled modes.\textsuperscript{51} One study evaluated patients who used HMV devices with either pressure controlled or pressure support ventilation.\textsuperscript{47} Three studies evaluated patients who used CPAP devices.\textsuperscript{65, 67, 70} CPAP equipment parameters included CPAP with spontaneous breathing.

Six studies reported the model and manufacturer of the device used.\textsuperscript{47, 51, 66-69} Three studies did not report the model or manufacturer of the device used.\textsuperscript{42, 65, 70} We did not report mask type used, use of a humidifier, or use of supplemental oxygen.

KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g. patient education, ongoing smoking cessation, respiratory therapist led home care)?

Key Points-KQ4

- Evidence is lacking to determine the effect of specific respiratory home services on outcomes.
- Respiratory services provided in the home included: lifestyle counseling by nurses.

Two studies described respiratory services provided in the home. These services included life style counseling by nurses.\textsuperscript{67, 68}

KQ5. What are the professional guidelines and statements which address KQ 1 to KQ 4?

Information related to clinical guidelines can be found in Appendix Table G.5.
Other Respiratory Diseases

Other respiratory diseases included cystic fibrosis, bronchiectasis, and interstitial lung disease. Two studies\(^42,\,71\) with a total of 42 patients were included. The characteristics of the studies are listed in Appendix Table D.1. 1 evaluated HMV\(^71\), 1 BPAP, \(^42\) and 0 CPAP. These studies were conducted in the United States (n=0), Canada (n=0), Europe (n=1), and other countries (n=1). We also identified 3 clinical practice guidelines relevant to KQ1-4(Appendix Table G.6.).\(^76,\,77,\,86,\,92\)

Overall risk of bias was rated as moderate due to selective patient population and unclear risk of conflict of interest in the observational studies(Appendix Table E.1 and E.2.).

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bilevel Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface?

Key Points-KQ1

- The criteria used to start NIPPV were variable but most commonly included: diagnosis of diffuse parenchymal lung disease and/or bronchiectasis, hypoxia, and/or hypercapnia.
- No studies compared the initiation criteria between different devices or evaluated criteria for device continuation.
- Processes used to titrate NIPPV were variable with the following targets used: reduction in hypercapnia, reduction in hypoxia (including nocturnal hypoxia), and achievement of target tidal volumes.

Two described criteria for initiation of HMV, BPAP, and/or CPAP devices in patients with other lung diseases.\(^42,\,71\)

Disease diagnosis

Studies enrolled patients with diffuse parenchymal lung diseases\(^42\) and diffuse bronchiectasis.\(^71\)

Other characteristics

One study enrolled patients with hypoxemia and hypercapnia NOS\(^42\) and a second study enrolled patients already on home HMV and LTOT.\(^71\)

Targets of device titration

Targets of device titration included “desired tidal volume”\(^42\) and normal PaO2 mmHg without deterioration in PaCO2.\(^71\)
Device continuation

No studies described criteria for device continuation.

KQ2. What is the effect of HMV, a BPAP, or a CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

Key Points-KQ2

- Mortality, hospital admission, quality of life, or need for intubation was not evaluated.
- HMV (compared with no device) was associated with significantly shorter length of hospital stay in patients with bronchiectasis.

One case control study compared HMV (volume cycled) plus long-term oxygen therapy to long-term oxygen therapy only in 28 patients with diffuse bronchiectasis and severe chronic respiratory failure. The reduction of length of hospital stay in the HMV and long-term oxygen therapy group was significantly higher than those in the long-term oxygen therapy group (WMD=-42.00 days per year, 95% CI: -76.37 to -7.63). No significant difference was found on length of survival. Results are summarized in Table 15.

Table 15. Effectiveness of HMV vs. no device in patients with other respiratory diseases

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Conclusion</th>
<th>Study Design (sample size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMV vs. No Device</td>
<td>Length of survival</td>
<td>Median 45 months vs. 48 months, p&gt;0.05</td>
<td>1 Observational study (28 patients)</td>
</tr>
<tr>
<td></td>
<td>Length of hospital stay</td>
<td>WMD: -42.00; 95% CI: -76.37 to -7.63; p=0.02, I2=N/A</td>
<td>1 Observational study (28 patients)</td>
</tr>
</tbody>
</table>

CI: confidence interval, HMV: home mechanical ventilation, N/A: not applicable, WMD: weighted mean difference
KQ3. What are the equipment parameters that are used?  a) What are the parameters of ventilator usage (e.g. mode as determined by trigger, control and cycling variables)? b) What are the equipment parameters that are necessary to achieve desired outcomes (e.g. flow capabilities, settings, etc.)?  c) What are the parameters of prescribed patient usage (e.g. frequency of use, duration of use throughout the day, other)?  d) In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?

Key Points-KQ3

- The BPAP mode utilized was BPAP ST
- The HMV mode utilized was volume assist control ventilation mode.

One study evaluated patients who used BPAP ST. BPAP ST equipment parameters included IPAP, EPAP, and a spontaneous/timed (ST) breathing mode with a backup respiratory rate. One study evaluated patients who used HMV, volume assist control ventilation. No studies reported the model or manufacturer of the device used. We did not report mask type used, use of a humidifier, or use of supplemental oxygen.

KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g. patient education, ongoing smoking cessation, respiratory therapist led home care)?

No studies described respiratory services provided in the home.

KQ5. What are the professional guidelines and statements which address KQ 1 to KQ 4?

Information related to clinical guidelines can be found in Appendix Table G.6.
Mixed Disease Conditions

Mixed disease conditions included cohorts of patients with one or more of the above described disease conditions. Five studies with a total of 331 patients were included. The characteristics of the studies are listed in Appendix Table D.1. Four evaluated HMV, one BPAP, and zero CPAP. These studies were conducted in the United States (n=0), Canada (n=0), Europe (n=4), and other countries (n=1). We also identified six clinical practice guidelines relevant to KQ1-4 (Appendix Table G.1.).

Overall risk of bias was rated as moderate. The RCTs were unable to blind patients, providers, or outcome assessors, and had unclear risk of allocation concealment (Appendix Table E.1.). The observational studies were found to have selective patient population, and high risk of outcome assessment in observational studies (Appendix Table E.2.).

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bilevel Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface.

Key Points-KQ1

- The criteria used to start NIPPV were variable but most commonly included PaCO2 > 45 mmHg, hypoxia, and/or pH ≥ 7.35.
- HMV started in the home setting compared to HMV started in the hospital was not associated with differences in mortality or quality of life (in patients with NMD or TRD).
- No major differences were found in the criteria used to initiate a BPAP or a HMV device.
- Processes used to titrate NIPPV were variable with the following targets used: reduction in hypercapnia, reduction in hypoxia, and achievement of target tidal volumes.

Five studies described criteria for initiation and/or continuation of HMV, BPAP, and/or CPAP devices in patients with mixed respiratory diseases. Four studies evaluated patients who had not yet started home device use and one study. There were no major differences in criteria used to start BPAP versus HMV.

Disease diagnosis

Studies enrolled patients with TRD, OHS, NMD, COPD, and Other.

Other characteristics

Studies used the following laboratory criteria for enrollment: pH ≥ 7.35 (7100), PaCO2 > 45 mmHg, PaCO2 > 50 mmHg, nocturnal SaO2 < 88% for ≥ 5 consecutive minutes.
Stable disease versus acute exacerbation

One study enrolled patients who started home NIPPV during or shortly after acute exacerbation\(^\text{74}\) and 3 studies enrolled patients with stable disease (no current or recent exacerbation)\(^\text{34, 72, 73}\).

Targets of device titration

Most studies reported using maximum tolerated respiratory pressures (such as IPAP and/or EPAP) needed to achieve the following stated goals: maximum decrease in PaCO\(_2\), tidal volume of 8-10mL/kg, normalization of PaO\(_2\).

Device continuation

No studies described criteria for device continuation.

KQ2. What is the effect of HMV, a BPAP, or a CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

Key Points-KQ2

- BPAP (compared with no device) was associated with reduced hospital admissions (SOE: low) in patients with COPD, asthma, or bronchiectasis.

In one RCT, 37 severe hypercapnic obstructive lung diseases (chronic obstructive pulmonary disease (COPD), asthma, and bronchiectasis) were randomized to receive BPAP or standard treatment.\(^\text{74}\) Patients in the BPAP group was found to have significantly better outcomes on 6-minute walk distance (WMD: 99.80; 95% CI: 34.14 to 165.46; p<0.01), number of hospitalization per patient (WMD: -2.30; 95% CI: -3.36 to -1.24; p<0.001), and length of hospital stay (WMD: -37.70; 95% CI: -57.68 to -17.72; p<0.001). There was no statistical difference between the two groups on resting Borg score and Borg score at end of 6-minute walk test. 4 patients from the BPAP group withdrew from the study due to intolerance of BPAP device.

One retrospective observational study compared HMV volume assist control ventilation to HMV volume control in patients with NMD or TRD.\(^\text{73}\) There was no statistically significant difference on mortality (OR= 0.91, 95% CI: 0.28 to 2.96, p=0.88), and number of hospital admissions (0.17 per patient in HMV volume assist/control mode vs. 0.04 per patient in HMV volume control mode, p=0.11).

In one RCT, 77 patients with NMD or TRD were randomized to start HMV at home or start HMV in the hospital.\(^\text{72}\) There was no significantly difference on mortality (OR=2.80, 95% CI:...
0.51 to 15.43), or quality of life (Severe Respiratory Insufficiency, SF-36) between the two groups.

Comparative effectiveness evidence with SOE rating for major outcomes is summarized in Table 16. Other outcomes are summarized in Table 17.

### Table 16. Major effectiveness outcomes with SOE (all devices in studies with mixed disease conditions)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Conclusion</th>
<th>Study Design (sample size)</th>
<th>Rationale for Strength of Evidence (SOE)</th>
<th>Overall Evidence Strength (Direction of Effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAP vs. no device</td>
<td>Number of hospitalization per patients</td>
<td>-2.30; 95% CI -3.36 to -1.24; I²=N/A</td>
<td>1 RCT (37 patients)</td>
<td>Imprecision</td>
<td>Low (reduction with BPAP)</td>
</tr>
<tr>
<td>HMV volume assist control ventilation vs. HMV volume control</td>
<td>Mortality</td>
<td>OR: 0.91, 95% CI: 0.28 to 2.96, p=0.88 9 fewer per 1000 patients (116 fewer to 99 more)</td>
<td>1 RCT (126 patients)</td>
<td>Severe imprecision</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Number of hospital admissions</td>
<td>Rate ratio: 4.25, p=0.11; Follow up: 12 months</td>
<td>1 RCT (126 patients)</td>
<td>Severe imprecision</td>
<td>Insufficient</td>
</tr>
<tr>
<td>HMV started at home vs. HMV started in the hospital</td>
<td>Mortality</td>
<td>OR: 2.80, 95% CI: 0.51 to 15.43 80 more per 1000 patients (48 fewer to 208 more)</td>
<td>1 RCT (77 patients)</td>
<td>Severe imprecision</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Quality of life (Severe Respiratory Insufficiency, SF-36)</td>
<td>No statistical difference on all domains</td>
<td>1 RCT (77 patients)</td>
<td>Severe imprecision</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

BPAP: bi-level positive airway pressure, CI: confidence interval, HMV: home mechanical ventilation, N/A: not applicable, OR: odds ratio, RCT: randomized controlled trial, SF-36: Medical Outcomes Study Questionnaire Short Form, WMD: weighted mean difference

### Table 17. Other effectiveness outcomes (all devices in studies with mixed disease conditions)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Conclusion</th>
<th>Study Design (sample size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAP vs. no device</td>
<td>6-minute walk distance test (meters)</td>
<td>WMD: 99.80; 95% CI: 34.14 to 165.46; I²=N/A</td>
<td>1 RCT (37 patients)</td>
</tr>
<tr>
<td></td>
<td>Length of hospital stay (days)</td>
<td>-37.70; 95% CI: -57.68 to -17.72; I²=N/A</td>
<td>1 RCT (37 patients)</td>
</tr>
</tbody>
</table>

BPAP: bi-level positive airway pressure, CI: confidence interval, HMV: home mechanical ventilation, N/A: not applicable, OR: odds ratio, RCT: randomized controlled trial, SF-36: Medical Outcomes Study Questionnaire Short Form, WMD: weighted mean difference
KQ3. What are the equipment parameters that are used? a) What are the parameters of ventilator usage (e.g. mode as determined by trigger, control and cycling variables)? b) What are the equipment parameters that are necessary to achieve desired outcomes (e.g. flow capabilities, settings, etc.)? c) What are the parameters of prescribed patient usage (e.g. frequency of use, duration of use throughout the day, other)? d) In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?

**Key Points-KQ3**
- BPAP devices used mode BPAP NOS (unclear if S or ST)
- For HMV devices, the modes utilized were pressure controlled ventilation, volume assist control ventilation, volume control ventilation, and pressure/volume controlled ventilation NOS.

One study evaluated patients who used BPAP NOS (unclear if ST or S mode). Four studies evaluated patients who used HMV devices. HMV modes utilized were pressure controlled ventilation, volume assist control ventilation, volume control ventilation, and pressure or volume controlled ventilation NOS. No studies evaluated CPAP use.

Two studies reported the model and manufacturer of the device used. Three studies did not report the model or manufacturer of the device used. We did not report mask type used, use of a humidifier, or use of supplemental oxygen.

KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g. patient education, ongoing smoking cessation, respiratory therapist led home care)?

**Key Points-KQ4**
- Evidence is lacking to determine the effect of specific respiratory home services on outcomes.
- Respiratory services provided in the home included: telephone hotline and scheduled phone calls

Two studies described respiratory services provided in the home which included a telephone hotline staffed by healthcare professionals including nurses, respiratory therapists, and/or others, and scheduled phone calls by respiratory therapists every 2 weeks to ensure compliance.
KQ5. What are the professional guidelines and statements which address KQ 1 to KQ 4?

Information related to clinical guidelines can be found in Appendix Table G.1.
Adverse Events

Key Points - Adverse Events

- Only 19 out of the 61 included studies (31.15%) evaluated adverse events. A majority of these studies did not use a consistent approach for evaluation and reporting.
- Serious events (such as mortality, hospitalization, and need for intubation) were commonly classified as study outcomes and were infrequently and non-uniformly classified as serious adverse events.
- The pooled incidence of reported non-serious adverse events was 0.35 for HMV, 0.31 for BPAP, 0.27 for HMV/BPAP mix, 0.39 for CPAP, and <0.001 for no device groups.
- The pooled incidence of reported serious adverse events was <0.001 for HMV, 0.01 for BPAP, 0.09 for CPAP, and <0.001 for no device groups.
- Based on direct comparisons, we found no statistically significant differences in total number of treatment withdrawals or adverse events (serious plus other) when comparing different devices or when comparing device use with no device use.

42 out of the 61 included studies (68.85%) did not evaluate adverse events and a majority of the rest of the studies did not use a consistent approach for evaluation and reporting. Serious events (such as mortality, hospitalization, and need for intubation) were commonly classified as study outcomes and were infrequently and non-uniformly classified as serious adverse events.

19 studies (12 RCTs15, 18-20, 23, 24, 27, 29, 44, 65, 67, 68, 74, 82 and 725, 26, 33, 49, 50, 73, 75 observational studies) reported a total of 264 adverse events in 1297 patients. Table 3 presents the description of the adverse events categories. Table 18 shows the pooled incidence rate of adverse events by device.

<table>
<thead>
<tr>
<th>Device</th>
<th>Serious adverse events incidence rate and 95% CI</th>
<th>Non-serious adverse events incidence rate and 95% CI</th>
<th>Total adverse events incidence rate and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMV</td>
<td>IR: 0.00; 95% CI: 0.00 to 0.00</td>
<td>IR: 0.35; 95% CI: 0.27 to 0.46</td>
<td>IR: 0.35; 95% CI: 0.27 to 0.46</td>
</tr>
<tr>
<td>BPAP</td>
<td>IR: 0.01; 95% CI: 0.00 to 0.05</td>
<td>IR: 0.31; 95% CI: 0.16 to 0.58</td>
<td>IR: 0.31; 95% CI: 0.23 to 0.36</td>
</tr>
<tr>
<td>HMV/BPAP mix</td>
<td>Not reported/not evaluated</td>
<td>IR: 0.27; 95% CI: 0.15 to 0.50</td>
<td>IR: 0.27; 95% CI: 0.16 to 0.42</td>
</tr>
<tr>
<td>CPAP</td>
<td>IR: 0.09; 95% CI: 0.03 to 0.26</td>
<td>IR: 0.39; 95% CI: 0.27 to 0.56</td>
<td>IR: 0.39; 95% CI: 0.25 to 0.49</td>
</tr>
<tr>
<td>No device</td>
<td>IR: 0.00; 95% CI: 0.00 to 0.01</td>
<td>IR: 0.00; 95% CI: 0.00 to 0.00</td>
<td>IR: 0.00; 95% CI: 0.00 to 0.00</td>
</tr>
</tbody>
</table>

BPAP: bi-level positive airway pressure, CI: confidence interval, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, IR: incidence rate

The pooled incidence rate of non-serious adverse events was <0.001 in patients with no device use and ranged from 0.27-0.39 in patients using HMV, BPAP, and CPAP devices. The most common non-serious adverse events included skin symptoms (e.g. facial rash, nasal ulceration), eye symptoms (e.g. dry eyes, conjunctivitis), nose/mouth symptoms (e.g. nasal stuffiness, rhinorrhea, nosebleed, mucosal dryness, oral air leak), gastrointestinal symptoms (e.g. gastric distension, aerophagia), and device/mask intolerance (e.g. clausrophobia, discomfort, noncompliance).

The pooled incidence rate of serious adverse events was <0.001 in HMV, 0.01 in BPAP, 0.09 in CPAP, and <0.001 in patients using no device. The types of serious adverse events are listed...
in Table 19. Death, hospitalization, and intubation were reported as primary efficacy outcomes. The most commonly reported serious adverse event was acute respiratory failure.

Table 19. Types of reported serious adverse events

<table>
<thead>
<tr>
<th>Device type</th>
<th>Serious adverse events</th>
<th>Number of cases, patients at risk, and studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAP</td>
<td>Acute respiratory failure</td>
<td>29 cases out of 178 patients (5 studies) 563, 593, 739, 6699, 6830</td>
</tr>
<tr>
<td></td>
<td>Treatment failure (combined endpoint of use&lt;2h/night, hospital admission for respiratory failure, or PaCO₂&gt;60)</td>
<td>4 cases out of 29 patients (1 study) 122</td>
</tr>
<tr>
<td></td>
<td>Aortic dissection</td>
<td>1 case out of 37 patients (1 study) 287</td>
</tr>
<tr>
<td></td>
<td>Transient ischemic attack</td>
<td>1 case out of 23 patients (1 study) 639</td>
</tr>
<tr>
<td>CPAP</td>
<td>Treatment failure (combined endpoint of use&lt;2h/night, hospital admission for respiratory failure, or PaCO₂&gt;60)</td>
<td>4 cases out of 31 patients (1 study) 122</td>
</tr>
<tr>
<td>HMV</td>
<td>Not reported/not evaluated</td>
<td></td>
</tr>
<tr>
<td>HMV/BPAP mix</td>
<td>Not reported/not evaluated</td>
<td></td>
</tr>
<tr>
<td>No device</td>
<td>Acute respiratory failure</td>
<td>13 cases out of 30 patients (2 studies) 6830, 739</td>
</tr>
<tr>
<td></td>
<td>Ischemic stroke</td>
<td>1 case out of 35 patients (1 study) 287</td>
</tr>
<tr>
<td></td>
<td>Arrhythmia requiring pacemaker</td>
<td>1 case out of 18 patients (1 study) 6699</td>
</tr>
</tbody>
</table>

Table 20 summarizes the direct comparisons of total number of adverse events and withdrawals by device and disease reported by individual studies. We found no statistically significant difference in withdrawals and total number of adverse events when comparing devices or when comparing device use with no device use.

Table 20. Comparisons of total number of adverse events by devices and diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Comparison</th>
<th>Adverse events</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>BPAP vs. no device</td>
<td>Total number of withdrawals                                                   OR: 1.17; 95% CI: 0.59 to 2.33; I²=53.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total number of adverse events                                                Rate Ratio: 1.16, 95% CI: 0.23 to 5.73; I²=71.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BPAP IVAPS vs. BPAP ST</td>
<td>Total number of withdrawals                                                   OR: 1.00; 95% CI: 0.18 to 5.67; I²=N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total number of adverse events                                                Rate Ratio: 2 cases in BPAP IVAPS and 0 case in BPAP ST</td>
<td></td>
</tr>
<tr>
<td>NMD</td>
<td>HMV vs. BPAP</td>
<td>Total number of withdrawals                                                   OR: 2.44; 95% CI: 0.61 to 9.86, I²=N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total number of adverse events                                                Rate Ratio: 0 in both groups</td>
<td></td>
</tr>
<tr>
<td>OHS</td>
<td>HMV/BPAP mix (all with bilevel pressure with assured volume) vs. no device</td>
<td>Total number of withdrawals                                                   OR: 0.69; 95% CI: 0.25 to 1.88, I²=N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total number of adverse events                                                Rate Ratio: 0.69; 95% CI: 0.39 to 1.22; I²=N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HMV/BPAP mix (all with bilevel pressure with assured volume) vs. CPAP</td>
<td>Total number of withdrawals                                                   OR: 0.56; 95% CI: 0.27 to 1.33; I²=N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total number of adverse events                                                Rate Ratio: 32 non serious adverse in CPAP and 0 non serious adverse in no device</td>
<td></td>
</tr>
<tr>
<td>CPAP</td>
<td>vs. no device</td>
<td>Total number of withdrawals                                                   OR: 3.56; 95% CI: 0.95 to 13.33; I²=N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total number of adverse events                                                Rate Ratio: 32 non serious adverse in CPAP and 0 non serious adverse in no device</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BPAP vs no device</td>
<td>Total number of withdrawals                                                   OR: 0.94; 95% CI: 0.06 to 16.33; I²=N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total number of adverse events                                                Rate Ratio: 0.95; 95% CI: 0.06 to 15.15; I²=N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BPAP vs. CPAP</td>
<td>Total number of withdrawals                                                   OR: 2.22; 95% CI: 0.19 to 25.91; I²=N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total number of adverse events                                                Rate Ratio: 2.22; 95% CI: 0.19 to 25.91; I²=N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NMD</td>
<td>Total number of withdrawals                                                   Rate Ratio: 1.07; 95% CI: 0.27 to 4.27; I²=N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1) HMV volume assist/control mode</td>
<td>Total number of adverse events                                                Rate Ratio: 1.19; 95% CI: 0.63 to 2.26; I²=N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2) HMV volume control mode</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>COPD, and other</td>
<td>Total number of withdrawals                                                   OR: 1.62; 95% CI:0.37 to 7.05; I²=N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total number of adverse events                                                Rate Ratio: 19 cases in BPAP vs. 0 case in no device</td>
<td></td>
</tr>
</tbody>
</table>

48
BPAP: bi-level positive airway pressure, CI: confidence interval, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, NMD: neuromuscular diseases, OHS: obesity hypoventilation syndrome

*: Only studies reported direct comparisons between devices or between device use with no device use were evaluated in this table.
Discussion

Overview

We conducted a systematic review to assess the effectiveness of home NIPPV (using HMV, BPAP, and/or CPAP devices) in adults with chronic respiratory failure. We assessed the criteria considered for initiation and continuation of home NIPPV, respiratory services provided in the home, adverse events, and summarized relevant clinical practice guidelines.

When evaluating patients with chronic respiratory failure who may benefit from NIPPV in the home setting, key clinical considerations include 1) when to start NIPPV and 2) which device type (HMV vs. BPAP) and device mode are needed to deliver acceptable and safe ventilation. These considerations may vary based on the underlying etiology of chronic respiratory failure (COPD vs. thoracic restrictive disease vs. neuromuscular diseases vs. obesity hypoventilation vs. other). In general, included studies evaluated the efficacy of starting chronic home NIPPV in patients with moderate to severe stable disease and/or patients with unstable disease in current acute respiratory exacerbation.

Figure 3 summarizes the distribution of evidence for device effectiveness by disease conditions. Most of the evidence concentrated on the comparison between BPAP and no device in patients with COPD, while comparisons between devices and other conditions were scarce.
Figure 3. Evidence map for effectiveness of device use.

Table 21. Summary of device effectiveness in patients with COPD

<table>
<thead>
<tr>
<th>Device</th>
<th>Comparator(s)</th>
<th>Findings (Strength of evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMV</td>
<td>individually with BPAP, CPAP, or no device</td>
<td>Fewer hospital admissions (low SOE)</td>
</tr>
<tr>
<td>HMV</td>
<td>no device</td>
<td>No difference in mortality (insufficient SOE)</td>
</tr>
<tr>
<td>BPAP</td>
<td>no device</td>
<td>Lower mortality (moderate SOE)</td>
</tr>
<tr>
<td>BPAP volume assured pressure support ventilation</td>
<td>BPAP ST</td>
<td>No difference in mortality (insufficient SOE) and quality of life (insufficient SOE)</td>
</tr>
</tbody>
</table>
### Table 21. Summary of device effectiveness in patients with thoracic restrictive diseases

<table>
<thead>
<tr>
<th>Device</th>
<th>Comparator(s)</th>
<th>Findings (Strength of evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMV pressure controlled ventilation</td>
<td>HMV pressure support ventilation</td>
<td>No difference in quality of life (insufficient SOE)</td>
</tr>
</tbody>
</table>

BPAP: bilevel positive airway pressure, CPAP: continuous positive airway pressure, HMV: home mechanical ventilator, ICU: intensive care unit, SOE: strength of evidence, ST: spontaneous/timed mode

### Table 22. Summary of device effectiveness in patients with thoracic restrictive diseases

<table>
<thead>
<tr>
<th>Device</th>
<th>Comparator(s)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMV</td>
<td>no device</td>
<td>Lower mortality (low SOE)</td>
</tr>
</tbody>
</table>

HMV: home mechanical ventilator, SOE: strength of evidence

### Table 23. Summary of device effectiveness in patients with neuromuscular disease

<table>
<thead>
<tr>
<th>Device</th>
<th>Comparator(s)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAP</td>
<td>no device</td>
<td>Lower mortality (low SOE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Better quality of life (low SOE)</td>
</tr>
</tbody>
</table>

BPAP: bilevel positive airway pressure, HMV: home mechanical ventilator, SOE: strength of evidence

### Table 24. Summary of device effectiveness in patients with obesity hypoventilation syndrome

<table>
<thead>
<tr>
<th>Device</th>
<th>Comparator(s)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMV/BPAP mix</td>
<td>no device</td>
<td>No difference in exercise tolerance or quality of life (insufficient SOE)</td>
</tr>
<tr>
<td>HMV/BPAP mix</td>
<td>CPAP</td>
<td>No difference in sleep quality or quality of life (insufficient SOE)</td>
</tr>
<tr>
<td>CPAP</td>
<td>no device</td>
<td>No difference in exercise tolerance or quality of life (insufficient SOE)</td>
</tr>
<tr>
<td>BPAP</td>
<td>CPAP</td>
<td>No difference in hospital admissions (insufficient SOE), and quality of life (insufficient SOE)</td>
</tr>
</tbody>
</table>

BPAP: bilevel positive airway pressure, CPAP: continuous positive airway pressure, HMV: home mechanical ventilator, SOE: strength of evidence

### Table 25. Summary of device effectiveness in patients with other respiratory diseases

<table>
<thead>
<tr>
<th>Device</th>
<th>Comparator(s)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMV</td>
<td>no device</td>
<td>Mortality, hospital admission, quality of life, or need for intubation was not reported. shorter length of hospital stay</td>
</tr>
</tbody>
</table>

HMV: home mechanical ventilator, SOE: strength of evidence. Other respiratory diseases included cystic fibrosis, bronchiectasis, and interstitial lung disease.

### Table 26. Summary of device effectiveness in patients with mixed disease conditions

<table>
<thead>
<tr>
<th>Device</th>
<th>Comparator(s)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAP</td>
<td>no device</td>
<td>Fewer hospital admissions (low SOE)</td>
</tr>
</tbody>
</table>

BPAP: bilevel positive airway pressure, SOE: strength of evidence. Mixed disease conditions included cohorts of patients with one or more of COPD, thoracic restrictive diseases, neuromuscular disease, obesity hypoventilation syndrome, or other respiratory diseases.

We found no major differences in the criteria considered for initiation of a HMV versus BPAP device—and included studies did not directly address this clinical question. The most common criteria for initiation of home NIPPV using a HMV and/or BPAP device were 1) COPD (FEV1<50% normal, PaCO2 >45mmHg, pH>7.35, and/or hypoxia), 2) thoracic restrictive diseases (PaCO2>45mmHg, stable disease, and FVC<40% normal or MIP<60cmH2O, or nocturnal SaO2<88% for ≥ 5 consecutive minutes), 3) neuromuscular disease (PaCO2>45mmHg or FVC<50% or MIP <60cmH2O, or nocturnal SaO2 < 88% for ≥ 5 consecutive minutes), 4) obesity hypoventilation syndrome (BMI>30kg/m2, PaCO2>45mmHg, and other causes of hypercapnia ruled out), 5) other respiratory diseases (hypercapnia and hypoxia).

Respiratory services provided in the home were variable and included: telephone hotline, scheduled phone calls, home visits, smoking cessation, cough assistance instruction and devices,
and dietary and lifestyle counseling. Only one RCT evaluated the efficacy of home respiratory services and found that BPAP ST with weekly telemonitoring (compared with BPAP ST alone) in NMD patients was associated with fewer office visits, fewer emergency room visits, fewer hospital admissions, and no difference in mortality.

Serious and non-serious adverse events were reported in patients in the HMV, BPAP, CPAP, and no device groups. Incidence of non-serious adverse events (such as facial rash, mucosal dryness, mask discomfort, etc.) were approximately 0.30 across devices. Reported serious adverse events were rare. The most commonly reported serious adverse event was acute respiratory failure, which occurred in patients in using BPAP, CPAP, as well as patients using no devices. The recognition that patients using NIPPV devices may experience serious adverse events such as acute respiratory failure should be interpreted with the following considerations: First, reporting of serious adverse events was not uniform across studies, with a majority of studies not reporting serious adverse events and a majority of the remaining studies reporting no serious adverse events. Second, many studies that reported serious adverse events such as acute respiratory failure in patients who used NIPPV devices also reported that acute respiratory failure occurred, sometimes at even higher rates, in patients who used no devices. Third, outcomes such as death, hospitalization, and need for intubation were considered as primary efficacy outcomes and not serious adverse events. Therefore, recognition of serious adverse events should be balanced with efficacy data showing benefit in mortality, hospitalization, and need for intubation in many disease categories. Fourth, comparative studies found no statistically significant differences in adverse events or treatment withdrawals among device type (Table 19).

Findings in Relation to What Is Known

This systematic review provides evidence that in patients with nearly every disease condition, NIPPV was associated with both a statistically and clinically significant reduction in mortality. In addition, in patients with COPD, NIPPV was associated with fewer hospitalizations, fewer intubations, reduced dyspnea and no change in quality of life. In COPD, NIPPV via HMV (compared individually to BPAP, CPAP, or no device) was associated with fewer hospital admissions (SOE: low). For patients with TRD, NMD, OHS, and other lung diseases, NIPPV was also associated with improved exercise tolerance, improved quality of life, reduced dyspnea, improved sleep quality, and shorter length of hospital stay in individual populations. Published guidelines varied with regards to criteria used to start NIPPV, criteria used to titrate NIPPV, recommended equipment parameters to use in specific disease conditions, and recommended respiratory services, all with various levels of evidence. While many guidelines recommended initiation of home NIPPV for daytime hypercapnia (PaCO2 ≥ 45mmHg), some guidelines recommended initiation of home NIPPV prior to the development of daytime hypercapnia. In COPD, some guidelines recommend initiation of home NIPPV in patients with chronic daytime hypercapnia and/or recurrent episodes of acute hypercapnic respiratory failure, some guidelines cite insufficient evidence to recommend such practices.

While some guidelines recommended certain clinical circumstances when provision of an HMV was preferred to a BPAP machine, there is currently not convincing comparative evidence to support these recommendations. For example, two European guidelines recommended an HMV device with an alternative backup power source, alarms to signal “mask off” or “low pressure” or “power failure,” and a second backup ventilator for patients with any disease
condition whose device use approached >16 or >18 hours/day. Guidelines also recommend the volume controlled or volume cycled features of HMV machines when pressure controlled ventilation failed to prevent hypercapnia in NMD, TRD, and OHS and when patients with any condition had difficulty triggering inspiration. Our review also found significant heterogeneity in the specific patient characteristics used to initiate home NIPPV. While most studies used hypercapnia (commonly, but not always defined as PaCO2 ≥ 45mmHg) as one criteria to initiate home NIPPV, there were several other disease specific and variable criteria used to initiate home NIPPV. We found no existing comparative evidence to support guideline recommendations of using HMV when device use approached >16 hours/day.

Limitations

Despite conducting a comprehensive literature search, we were unable to find sufficient evidence to identify ideal criteria to initiate and continue home NIPPV via different devices (KQ1), optimized equipment settings (KQ3), or impact of home respiratory services (KQ4). Qualitative syntheses of these KQs were also limited by heterogeneity of the included studies (population, inclusion/exclusion criteria, targets and process of device titration, devices used, follow up length, length of use of device, and study design). Our findings were also limited by lack of standard reporting of the following characteristics: 1) device type (i.e., difficulty in differentiating HMV from BPAP), 2) device used (e.g., manufacturer and model), 2) key device characteristics (e.g., mode used), and 3) device titration protocol and targets. For effectiveness and adverse events of home NIPPV (KQ2), the majority of the studies evaluated BPAP and no device in stable COPD patients. The evidence for comparative effectiveness of different devices and different modes is scarce, as well as the evidence for conditions other than stable COPD (i.e., COPD after recent exacerbation, OHS, NMD, or TRD, etc). The evaluation of adverse events was also limited by the fact that most of the included studies did not evaluate adverse events and majority of the rest did not use a consistent approach for report and evaluation. We could not statistically evaluate publication bias because the number of studies included in a direct comparison was small (n<10). We judged included studies to have medium to high risk of bias because of possible conflicts of interests (i.e., funded by device manufacturers), lack of blinding in RCTs and lack of representativeness of patient population in observational studies.

Applicability

Several issues limit the applicability of the stated findings. First, included studies were conducted in various locations across the globe. The provision of home NIPPV in different countries may differ based on devices available, devices commonly used, titration protocols, guidelines for home device use, associated respiratory services included, and coverage/payment of home NIPPV. In addition, the classification of devices as either an HMV and/or BPAP machine may differ in the United States compared with other locations. Second, several devices used in the included studies were not FDA approved. Third, several devices used in the included studies were older models that may no longer be available. Fourth, there is no data on several newer devices developed in the past 5-10 years. Fifth, patients in randomized controlled trials may significantly differ from those encountered in practice.
Suggestions for Future Research

Future comparative research should define which patient populations would benefit from NIPPV delivered by a HMV compared to a BPAP device. Populations that may benefit from a HMV include patients who require daytime NIPPV for a certain number of hours, patients with continued hypercapnia despite maximal BPAP use, patients who have rapidly progressively disease, or patients who have experienced adverse events despite BPAP use. Such populations may benefit from the tighter ventilator parameters, modes, monitoring, alarm features, and a second back up ventilator as offered by use of an HMV device. Such evidence would improve clinician ability to determine which features and device types are optimal for specific patient populations. In addition, future comparative research should evaluate when to initiate NIPPV, especially evaluating the utility of starting NIPPV in patients with stable disease versus following an episode of acute decompensation. Furthermore, comparative research should define which patient populations would benefit from advanced BPAP modes such as volume assured pressure support compared with other BPAP modes. There is a need to determine the optimal targets and process of device titration.

Conclusion

In COPD, home BPAP (compared to no device) was associated with lower mortality, intubations, hospital admissions, and dyspnea. There was no change in quality of life (pooled analysis of 9 studies). HMV (compared individually with BPAP, CPAP, or no device) was associated with fewer hospital admissions. In thoracic restrictive diseases, home HMV (compared to no device) was associated with lower mortality and better exercise tolerance. In neuromuscular diseases, home BPAP (compared to no device) was associated with lower mortality, better quality of life, and reduced dyspnea. Current comparative evidence is not available to assess the impact of many device capabilities on patient outcomes. Criteria to initiate home NIPPV and home respiratory services vary and are not validated in comparative studies.
References


42. Salturk C, Karakurt Z, Takir HB, et al. Comparison of exercise capacity in COPD...


86. Davidson AC, Banham S, Elliott M, et al. BTS/ICS guideline for the ventilatory...

87. STATEMENTS Q. VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE.


Abbreviations and Acronyms

ADL Activities of daily living
AECOPD Acute exacerbation of chronic obstructive pulmonary disease
AHRF Acute hypercapnic respiratory failure
AHRQ Agency for Healthcare Research and Quality
ALS Amyotrophic lateral sclerosis
BMI Body mass index
BPAP Bi-level positive airway pressure
CI Confidence interval
cmH2O Centimeters of water (pressure)
CMS Centers for Medicare and Medicaid Services
COPD Chronic obstructive pulmonary disease
CPAP Continuous positive airway pressure
EPAP Expiratory positive airway pressure
EPC Evidence-based Practice Center
ER Emergency room
FDA Food and Drug Administration
FEV1 Forced expiratory volume in one second
FVC Forced vital capacity
HMV Home mechanical ventilators
ICU Intensive care unit
IPAP Inspiratory positive airway pressure
IR Incidence rate
IRR Incidence rate ratio
Kg Kilogram
KQ Key Question
LTACH Long term acute care facility
LTOT Long term oxygen therapy
m meters
MHRA Medicines and Healthcare Products Regulatory Agency
MIP Maximal inspiratory pressure
mL Milliliters
mmHg Millimeters of mercury
NA Not Available
NIPPV Non-invasive positive pressure ventilation
NMD Neuromuscular diseases
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOS</td>
<td>Not otherwise specified</td>
</tr>
<tr>
<td>OHS</td>
<td>Obesity hypoventilation syndrome</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PaCO2</td>
<td>Partial pressure of arterial carbon dioxide</td>
</tr>
<tr>
<td>PaO2</td>
<td>Partial pressure of arterial oxygen</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive end expiratory pressure</td>
</tr>
<tr>
<td>pH</td>
<td>Potential of hydrogen</td>
</tr>
<tr>
<td>PICOTS</td>
<td>Population, interventions, comparisons, outcomes, timing, and setting</td>
</tr>
<tr>
<td>Pimax</td>
<td>Maximal inspiratory mouth pressures</td>
</tr>
<tr>
<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</td>
</tr>
<tr>
<td>PtcCO2/TcCO2</td>
<td>Pressure of transcutaneous carbon dioxide</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RAD</td>
<td>Respiratory assist device</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>S</td>
<td>Spontaneous mode</td>
</tr>
<tr>
<td>SaO2</td>
<td>Arterial blood oxygen saturation</td>
</tr>
<tr>
<td>SF-36</td>
<td>Medical Outcomes Study Questionnaire Short Form</td>
</tr>
<tr>
<td>SMD</td>
<td>Standardized mean difference</td>
</tr>
<tr>
<td>SOE</td>
<td>Strength of evidence</td>
</tr>
<tr>
<td>ST</td>
<td>Spontaneous/timed breath mode</td>
</tr>
<tr>
<td>TRD</td>
<td>Thoracic restrictive diseases</td>
</tr>
<tr>
<td>VAPS</td>
<td>Volume assured pressure support</td>
</tr>
<tr>
<td>WMD</td>
<td>Weighted mean difference</td>
</tr>
</tbody>
</table>