**Reviewer's Comment and Author Response Worksheet**

| REVIEWER | AUTHOR RESPONSE |
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| **General Comments to the Author:**<br><br>**Reviewer 1 -** An excellent guideline! I have some suggestions to improve readability- please see comments under major comments.<br><br>**Reviewer 2** - This is a very well written guideline with a comprehensive literature review and sensible PICO questions addressing the most obvious clinical dilemmas.<br><br>**Reviewer 3** - I found these guidelines very clear, well-balanced and highly reflective of the current evidence in the area. The evidence cited and its interpretation is appropriate, without over-reaching.<br><br>They are titled Clinical Guidelines, and the recommendations made are very practical and actionable from a clinical perspective.<br><br>The authors have developed questions and provided evidence-based responses that are of immediate clinical use.<br><br>Importantly, the authors have highlighted these guidelines target a very specific patient population, and implementation of therapy requires specialized expertise and resources. These are important points given the limited and low certainty of evidence currently available. | |
| **Major Comments:**<br><br>**Reviewer #1 :**<br>1) Please place the 4 PICO questions near the front of the document. For instance, the PICO questions can be placed into page 5 in the paragraph labelled 'formulation of key clinical questions'. The current text in the paragraph labelled 'formulation of key clinical questions' is confusing and should be deleted. | The text in the paragraph in question has been modified. |

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| 2) It is confusing to label the PICO questions 1a and 1b and 2a and 2b. Please relabel the individual questions as PICO 1, 2, 3 and 4. | The table summarizing the PICO questions and recommendations now makes it clearer. We believe that the link between PICOs 1a and 1b, where only the "P" is different, warrants this labelling. We have modified 2a and 2b to 2 and 3. |
| 3) It would be fantastic, and improve readability, if the authors could add a summary table to the beginning of the document. This table would have 4 columns:<br>Column 1: PICO question<br>Column 2: Recommendation<br>Column 3: Strength of Recommendation<br>Column 4: Certainty of Evidence<br>(For an example of a summary table see Table 2 in Am J Respir Crit Care Med Vol 201, Iss 9, pp e56–e69, May 1, 2020) | The summary of recommendations was replaced with a summary table. |
| The conclusion for PICO 1a is that "In patients with stable severe COPD and chronic hypercapnic respiratory failure ($paCO_2$>52 mm Hg), we <u>suggest</u> long-term home NIV to improve survival. (weak/conditional recommendation, low certainty evidence)" . However, the review of evidence showed that 2 of 4 studies did not show an effect on survival. Page 11 states: "The data were found to be inconsistent and imprecise with inadequate statistical power in the two negative studies, and the overall quality of data was deemed low."<br><br>Given this conclusion from the review of the evidence, the recommendation provided by the CPG needs better justification.<br><br>5) Recommendation 1b is being driven by results from a single trial (Murphy), and the 2 negative trials are being discounted. Should this not be acknowledged in the document?<br><br>6) A section should be added near the end of the document describing potential limitations of this CPG. Some limitations that could be included are:<br>o One weakness of this CPG is that the literature searches are not described, and the results of the literature searches with final decisions on which studies were | The discussion was modified as follows. The data were found to be inconsistent and imprecise, and the overall quality of data was deemed low. However, mortality is an outcome with little potential for bias. Recommendations considered that in the two negative studies, statistical power was inadequate for this outcome and these studies were attributed lower value. On the other hand, mortality was the primary outcome in the positive studies thus giving them greater weight.<br><br>The weak recommendation is a reflection of this inconsistencies across studies.<br><br>The studies are discussed under the relevant outcome (hospitalizations) for this PICO, in the Expert panel discussion, in the Details of included studies section, and in Good practice points. I believe we did not "discount" the studies, but we made an effort to detail methodological differences that may have explained results. We have however added emphasis on this in the hospitalization section of PICO 1b. Moreover, the weak recommendation is a reflection of this inconsistencies across studies.<br><br>The literature search is outlined on page 5. |

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| included for each PICO are not described. This could be listed as a limitation within the document.<br>o A second weakness of this CPG is that the data were not synthesized in a meta-analytic fashion for each outcome. Thus, data across the different studies is not being aggregated to produce standardized mean differences, or risk ratios. This could be listed as a limitation within the document. | This limitation has been acknowledged in a new limitations section towards the end of the manuscript. |
| **Reviewer #2:**<br>My main query is on recommendation 3:<br><br>3. 'We suggest high-intensity non-invasive ventilation instead of low-intensity non-invasive ventilation to improve paCO2 in patients with COPD with chronic hypercapnic respiratory failure(persistent paCO2 > 52 mmHg). (weak/conditional recommendation, low certainty evidence.'<br><br>I think the meaning of high intensity could be better explained to readers, as this tend to vary between trials. While there is a quite a lot of evidence that low intensity NIV is less effective or ineffective, readers may struggle to decide whether to use high IPAP, high back up rates, or both at initiation of therapy. At one point in the document high IPAP is considered as >20 cmH2O. Many of the German studies on high intensity NIV used an inpatient period to acclimatise patients to high intensity settings. One can conclude it is sensible to avoid low intensity settings, and should aim to achieve CO2 control -it's possible those are 'good enough' settings.<br><br>Also starting patients on high pressures and high rates may make acclimatisation to NIV as an outpatient difficult, especially in those with hyperinflation. So, a few sentences of guidance on what 'high intensity' means in practice may help. And whether all patients need these settings if PCO2 control is achieved at a 'moderate' IPAP level and a back-up rate that does not equate to 'Timed' mode. | Thank you for this comment. We have added some text to better define high intensity ventilation and to provide guidance on how this should be initiated. |
| **Reviewer #3:**<br>In my opinion, the certainty of evidence and recommendation strength determined by the authors are | |

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| appropriate and reflective of the evidence. | |
| As one of the stated Target users, representation by an end-user and/or patient advocate would have added to the depth and applicability of the recommendations particularly around the importance and value of patient-orientated outcomes and values. I am pleased to note this short-coming has already been recognized and will be addressed in future updates. | We have corrected the inconsistency. |
| In the Summary of Recommendations and section recommendations, the paCO2 threshold used is >52 mmHg whereas throughout the remainder of the document ≥52 mmHg is used. This threshold should be consistent throughout. | It is not the most frequent, but one of the most frequent as stated in the text. More recent references now included. |
| Introduction, 2nd paragraph: are there any more recent citations than the currently used one (ref 12) regarding COPD being the most frequent indication for NIV in Europe. This reference is around 15 years old. | CO2 goals from the Kohnlein study that are quoted by the reviewer have been added in the panel discussion section to give the reader more data. In addition, |
| While the panel was understandably not in a position to set a specific target for the reduction in paCO2 with NIV given current evidence, is there any scope for providing more nuanced detail about some of the target that have been used rather than just stating "a substantial reduction". E.g. studies generally targeting normalization of CO2, or values <48mmHg or 20% reduction compared to baseline etc." | We have added some text to better define high intensity ventilation and to provide guidance on how this should be initiated in the relevant section.<br><br>Added: "though the latter may impact HRQOL, one of the outcomes reviewed" |
| A low value was placed on adverse effects for patient values and preferences for PICO 1a & b but a high value on HRQL. Are not these two potentially closely linked such that discomfort and side-effects may adversely affect HRQL? | Added as requested. |
| Around sentence 732, mention of the Duiverman study (2020) re in-hospital versus home NIV initiation would be appropriate. | The question of EPAP is an interesting one and a higher EPAP may be necessary either due to hyperinflation and auto-PEEP, to allow patient to trigger, or to counter expiratory flow limitation in COPD. Emergent data and technology may rapidly change practice. We would therefore prefer not to make any |
| The authors have been clear that these recommendations apply to a specific target group. Perhaps mention around line 1062 that, these guidelines do not apply to patients with concomitant OSA and | |

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| hence EPAP around 5cmH2O is generally appropriate. | unsupported recommendations in that regard. |
| **Minor Comments:**<br><br>**Reviewer #3 only:**<br>Line 235: spacing in 'failure(persistent $paCO_2$ > 52 mmHg'<br><br>Line 307 and 369: correct spelling of Kohnlein | <br><br><br>Corrected.<br><br><br>Corrected. |
| **Other Suggestions:**<br><br>**Reviewer #3 only:**<br><br>Apart from involving a patient or patient representative in the next review, the framework of these clinical guidelines appears very robust.<br><br>While some mention of this has occurred within these recommendations, perhaps a brief section specifically comparing and contrasting these recommendations to those of the ERS and ATS so clinicians have this information in one place. | <br><br><br><br><br><br><br><br><br>A section discussing this comparison has been added. |