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Title	Proportional-assist ventilation with load adjustable gain factors for mechanical ventilation: a cost-utility analysis
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Reviewer 1	Dr. Manuel Alberto Guerrero Gutierrez
Institution	Instituto Nacional de Cancerología
General comments (author response in bold)	Very good article. It is a different point of view than mechanical ventilation **Dear Dr. Gutierrez, many thanks for taking the time to review our manuscript. We are very pleased that you found it to be an interesting and useful analysis of methods for mechanical ventilation.**
Reviewer 2	Dr. Karissa Johnston
Institution	Broadstreet Health Economics and Outcomes Research
General comments (author response in bold)	Thank you very much for the opportunity to review this article, I found it to be clear and well-written, about an obviously timely matter. I have several relatively minor comments: **Dear Dr. Johnston, we appreciate the time that you have taken to review the manuscript and the constructive comments provided to improve it. We address each of your comments below.** - The meta-analysis is referred to throughout as "pragmatic," and I would appreciate clarity on how exactly this is characterized? The description in the appendix reads as fairly standard meta-analysis practice so I wondered if it was primarily due to the literature review being structured rather than systematic or if there were other features of note? **Readers typically understand a meta-analysis to be based on a systematic literature review and we did not want to imply that we had undertaken such an exercise and so choose to use the word pragmatic each time we mentioned the meta-analysis. You are correct in your assumption that the only major different here to a standard meta-analysis is that we undertook a structured literature review where one author screened the title and abstracts of the included references. The same was true for full-text review, although data extraction was performed independently by all authors (so three people) to ensure to the highest degree that we did not misrepresent the data.** **Particularly when other meta-analyses have been performed, a pragmatic meta-analysis will suffice to explore other outcomes of interest as a systematic review of past literature has already been performed and need only be updated with recent or excluded trials if deemed appropriate.** **The York Health Economics Consortium defines a pragmatic review as "one that adapts the conventional systematic review process to take into consideration limited time and/or resources available. This is usually achieved by applying additional limits to the search or eligibility criteria."** **Although our literature review was structured, we are confident that we did not miss any relevant RCTs or controlled trials in our meta-analysis.** **There are examples of pragmatic meta-analyses being published, such as (for the ventilation space) Potts JM. Noninvasive positive pressure ventilation: effect on mortality in acute cardiogenic pulmonary edema: a pragmatic meta-analysis. Pol Arch Med Wewn. 2009 Jun;119(6):349-53. PMID: 19694215.**

	- The key model inputs includes days in ICU and in hospital as well as parameters around extubabation and reintubation risk - how are those related? In particular, in probabilistic sensitivity analysis, would iterations with lower rates of extubation be naturally associated with more time in ICU, or are the parameters independent? **The parameters time on mechanical ventilation, time in ICU, and time in hospital are not independent but connected by logic that prevents time on mechanical ventilation being longer than time in ICU etc. These parameters are, though, independent of extubation and reintubation risk and you are correct that a higher rate of reintubation would result in a longer time on mechanical ventilation and in the ICU. We have added wording to this effect in the methods section of our manuscript. We thank you for bringing this item to our attention and we hope that the update we have made clarifies how we handled this in the model.** - I would appreciate seeing cost and QALY results disaggregated further (i.e. during initial ICU stay, general ward stay, post-discharge, to better understand the dynamics of one-year vs. 20-year time horizon **We are happy to provide these data for you and have added these to the manuscript. We have taken 6 days to reflect time on MV, 12 days for time in the ICU, and 45 days for time in hospital. Due to space restrictions, and in line with other reviewer comments, we are removing focus on the 20-year time horizon but including this as a scenario analysis.** - When the inputs were restricted to Canada-only data PAV+ became cost-saving rather than cost-effective -- why was this, what was driving the difference? **This was mainly driven by shorter time in ICU (-5 days), a slightly higher ICU mortality (15% vs. 13%), and lower tracheostomy rate for PAV+ in the Canadian study. This was the pilot study for the PROMIZING study that was performed by one of the manuscripts authors: Dr. Bosma. From her analyses, we know that mortality, when it occurred, was earlier in the PAV+ group than in the PSV group, leading to a much shorter time in ICU. This pilot study, though, only included 50 patients, 27 PAV+ and 23 PSV, and its size limits the conclusions that can be drawn. This is a major reason why we look to the pragmatic meta-analysis to inform the model. We have added aspects of this answer to the discussion to more fully account for the Canada-specific scenario analysis.** - Note that in addition to the 2 cited SLRs there is one other one, by Yang et al., published in 2020. The Yang review includes a very similar list of studies, but with one additional study - by Salama et al., and the Aguirre-Bermeo study is not included. The meta-analysis results reported by Yang are very similar to the results used in this analysis with one key exception of extubation. **Many thanks for bringing this to our attention, we have now read the paper and included it in our discussions. The Salama data we do not have in our analysis as it was only available as a congress abstract and did not report on the hospital length of stay and other outcomes of interest for our pragmatic meta-analysis. The results of their study do, though, appear to be aligned with other literature on PAV+.** - they report a relative risk of 1.16 for PAV+ as opposed to the 1.48 reported here.

	The Vijayaraghavan analysis cited by the present authors also reported a risk of *intubation* of 0.92, so a reciprocal rate of extubation would be ~1.09. Thus, it would seem at least on the surface that the value used here (which may be a fairly significant model input) is being estimated as more beneficial in this analysis than other similar analyses which may warrant further explanation and discussion -> add to scenario analyses. **Thanks once again for bringing this to our attention and we have included a scenario analysis to explore this input variation. We have, as you suggested, used the value of 1.16 for PAV+ but note that in an exchange of letters to the editors Ou-Yang et al., update their estimate to be a RR of 1.19 (https://ccforum.biomedcentral.com/articles/10.1186/s13054-021-03575-9). As this value lies between our base case and their initially published estimate, we did not find it necessary to also test this value. We hope that you agree with this but welcome your feedback if not.** **With regard to the Vijayaraghavan analysis, this is a study that is well know to us and has extracted data from the Bosma study incorrectly. We have contacted the author directly about this as they are known to our authorship team, but to date no correction has been forthcoming. We are not inclined to use this data in our model at this time give that we are aware of inconsistencies between the study data published and the meta-analysis data presented. We hope that this clarifies our use of data sources in the model to some degree.** - In addition to the one-way scenarios presented, I think that there are a couple of others that would be valuable. One would be potentially exploring the extubation odds ratio as described above, if there is some uncertainty around this value. A second one is around the utility value assumed on mechanical ventilation. The value of -0.39 (based on the EQ-5D) originates from the study by Vainiola et al., which also estimated a value of +0.29 when using the alternate 15D instrument (which is anchored below at 0 rather than allowing worse-than-death valuations). There have been prior analyses describing challenges in numerically evaluating the strength of worse-than-death health states (e.g Rand-Hendriksen et al. 2012 Med Dec Making, Gandhi et al. 2018 Value in Health). The assumption that time on MV is substantially worse than death seems likely to be a key model driver, and while the -0.39 value is arguably a reasonable base case to use, I think that more in-depth exploration of alternative values in scenario analysis would be an informative addition to its variation in the probabilistic analysis. **Many thanks for your suggestions, we are happy to have provided this as an additional scenario analysis in our manuscript.** **[Editorial note: We agree with the reviewer that it is helpful to provide additional scenario analyses, unless you can provide strong justification for not doing so.).** - Minor point, there appears to be a typo in ref #29 with the journal name incorporated into the authors **We have been through the references and corrected a couple of errors from our reference manager as well as a duplicate reference. Your eye for detail is very much appreciated in helping us to improve and perfect our manuscript.**
Reviewer 3	Dr. Ahmad von Schlegell
Institution	Trillium Health Partners

General comments (author response in bold)	Overall comments: Regarding the overall importance of mechanical ventilation has increased in importance with an aging population and during the covid epidemic. However, even in the best of times as one of the authors that were referenced in this article noted, that "we have never been able to agree on triggers of ventilator support", and this has accompanied a large variation in the need for ventilator support. Nowhere has this been more apparent than with COVID (Wunsch, et. al., 2020). The purpose of this paper is to deal with pressure assisted ventilation with a cost of $27,000 vs. usual care which is pressure support ventilation from a cost effectiveness perspective to maximize ICU utilization. **Many thanks for your timely review and we agree with your outlook on the current situation. We have added the suggested reference to help support our introduction.** Part of this analysis will require focusing on model parameters for the cost effective models. Patient cohort demographics were similar to individuals with covid in age, and not extremely different on worldwide basis for covid like illnesses which makes this generalizable in that regard. However, the reference efficacy rates don't take account recent literature on asynchrony. For example, asynchrony from big data analysis was associated with time of day, ventilation mode, ventilation settings, sedatives, and analgesics. A line about context maybe helpful, and the study also showed which strengthens their view point of protective ventilation strategies such as low tidal volume, low plateau pressure, and high PEEP were all significantly associated with risk of PVA's after adjusting for other risk factors in negative binomial regression models (Ge, et. al., 2021). Here asynchrony was not associated with mortality or VAE. I wonder whether this will change your analysis. **This is a very interesting area, and one that requires consideration. Given that our model was developed before the arrival of COVID-19 and that all the efficacy data informing the model are also in non-COVID-19 patients it is difficult to make any claims with certainty. In scenario analyses we considered what would happen if PAV+ mode had no impact on asynchrony and the results were not too far removed from the base case. This may indicate that other benefits of the technology outweigh or work in synergy to the observed impact on asynchrony. Furthermore, the study of Ge et al examines data from 7 patients with COVID-19 and considers non-invasive mechanical ventilation. We would argue that at this time the level of data on asynchrony in COVID-19 patients on invasive mechanical ventilation (as modelled here) is not yet sufficient for a health-economic analysis.** In Table 1, PSV machines have $0 costs, and that isn't the case so it should include what the actual costs are for this machine at baseline to do a proper cost effectiveness analysis. This is an incremental cost effectiveness analysis with partial information. This was not explained. **Thank you for this bringing this to our attention, and we have corrected this omission on our part by including the following text in the methods "We assume that PSV mechanical ventilation is already available in the hospital, and so our analysis focuses on the incremental cost-utility of introducing PAV+ mode." Additionally, we refer to the incremental cost effectiveness ratio (ICER) as the outcome measure and include a scenario analysis where PSV is at cost to the hospital.**

	The other confounding issue is that total time is only significant with hospital length of stay, and as Bagwell recently noted, potentially avoidable delays in ICU discharge occurred in approximately 7 out of 10 patients in Canada had delayed transfers to ward, and the delay exceeded 24 hours for 1 in 4 patients (Bagwell, et. al., 2020). This is particularly important confounder as the driver for the ICER in this article is hospital length of stay. Other variables in the base case example don't reach statistical significance based on their 95% confidence intervals. I suspect the reason why Canada has been selected for this study is small number of hospitals per capita which is an indirect effect of the low number of both intensive care beds (12.9/100,000), and hospital beds per capita(2.5/1000) from the OECD. Hospital length of stay is increased, I believe from the contextual factors associated with where the ecology of care is delivered. However, to counter this issue, probabilistic analysis was done with previous work from one of the authors in this paper which the results of health state utility were based which dealt with parameter uncertainty, but there may be some structural uncertainty. However, similar cost effectiveness analysis held up with US and UK as well. **You are certainly correct that length of stay reduction is a major driver of outcomes with PAV+ mode. We do perform a Canada-specific scenario analysis, this analysis uses data from a pilot RCT undertaken in Canada. Here, the reduced length of ICU stay, (-5.1 days) was a key driver of cost outcomes. That reduced length of stay is observed in Canada as in other countries may indicate that time savings are achievable even if there is current delayed discharge from the ICU.Without building the model again from scratch it is difficult to assess the impact of structural uncertainty on the model outcomes. Given that other groups and other methodologies have reported similar outcomes for adaptive methods of mechanical ventilation, e.g. Hjelmgren J, Bruce Wirta S, Huetson P, Myrén KJ, Göthberg S. Health economic modeling of the potential cost saving effects of Neurally Adjusted Ventilator Assist. Ther Adv Respir Dis. 2016 Feb;10(1):3-17, and that our cost outcomes are in line with actual costing research from Canada (Hill AD, Fowler RA, Burns KEA, Rose L, Pinto RL, Scales DC. Long-Term Outcomes and Health Care Utilization after Prolonged Mechanical Ventilation. Ann Am Thorac Soc. 2017;14(3):355-362) we believe it is reasonable to consider the model to be valid for the analyses undertaken.** The adverse event rates are for tracheostomies, ventilator associated pneumonias, nosocomial infections, ICU mortality, and hospital mortality. I should mention that if covid increased demand for ICU ventilation, the associated tracheostomy literature that was cited in this paper would change as literature in recent Lancet by McGrath recommends that tracheostomies be delayed until day 10 of ICU stay because of viral infection loads (McGrath, et. al, 2020). I suspect that costs associated with VAP are also uncertain because of the uncertain epidemiology of COVID. This is part of the structural uncertainty that authors may or may not want to address as a line to differentiate this issue in the cost effectiveness analysis. **This is another interesting and as yet unknown aspect of how APV+ mode ventilation may interact with the current COVID-19 pandemic. With regard to tracheostomy rates, please note (as per Figure 1) that the model starts after patient stabilization in ICU and on MV and so it is uncertain where day 10 for the patient would be. We do explore the impact of tracheostomy in the**

	scenario analysis where only significant differences in outcomes are included (Table 3). Here PAV+ mode is still likely to be cost effective. From a methodological perspective, the paper is very good. Model outputs, inputs, time horizon, discounting, and statistical analysis are done well. The QALY gain is very small, but it doesn't appear worse, and if it is cheaper, then we should do it. There is some parameter uncertainty associated with long time horizons but other papers in this area have 40 year time horizons and I would also mention structural uncertainty should be discussed. Overall, it is a very good paper, and if the corrections are made and analysis stays the same I would conditionally accept. These include figure 2 below and the summary table to clarify which was part of the analysis, and if the results stayed the same. Hopefully, this computational approach will lend evidence for further cost collection and randomized trials in the future to validate these findings. **As per your comment above, structural uncertainty has been added to our discussion section. In line with other reviewer comments, the long-term time horizon has been restricted to a scenario analysis and as such forms a lesser part of the update manuscript.** Other edits: Reference 33, Line 373 has initials for reference titles, and it is repeated in reference 18. **Thank you for bringing this to our attention, we have now been through the references and removed a few typos and inconsistencies.** Figure 2 – ICU mortality PAV + shows 6 events and PSV shows 52 events and skews the figure to the right which is different than other graphs. ICU mortality on the summary results shows PAV + 29 events, and PSV events of 38 based on the same corresponding summary table from the graph. **We believe that this is a miss reading of the figure as part D of this figure is asynchrony and E is ICU mortality. Under instruction from the editorial team, this figure is now included in the supplement, but we have double checked the numbers and can confirm that they are correct.** Line 168 should read as something like there is increased costs of $1208 to $14,782 of cost savings. **Thank you, we hope to have reworded these sections in an appropriate manner now.** Line 52 Use of PAV+ mode is expected to benefit patient care in the ICU and be a cost-saving(1 year time horizon) or cost-effective(20 year time horizon) as an alternative to PSV **In line with other reviewer comments the 20-year time horizon is no longer a focus of the manuscript. We do agree that such rewording would have been beneficial.**