Author's response to reviews

**Title:** Informing advance directive discussions for patients with COPD at the point of care: A decision analysis.

**Authors:**

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**Version:** 4  **Date:** 18 November 2010

**Author's response to reviews:** see over
Dear Editor,

Thank you for the opportunity to address the peer reviewers comments and concerns. Below I have quoted the concerns and list individual responses to each. In addition, the manuscript has been edited with ‘tracked changes’ for your review, as per your request.

Thank you again for your time and consideration.

Sincerely,

Negin Hajizadeh
Referee # 2:

**Reviewer's report:**

“I am not sure why the authors did not enroll actual COPD patients in order to collect utilities and patient preferences from actual patients. This would have strengthened the research and shifted it from a theoretical framework towards an actual study of patient decisions.”

**Author’s Response:**

Our intent was to develop a decision model for advance directives that could accommodate a wide array of patient preferences, before pursuing actual patient preference elicitation. Once our decision analytic model is established the next phase of our research is to elicit patient preferences from a cohort of COPD patients.

We have made this more explicit by modifying the following in the Methods section:

**FROM:**

To inform the AD discussion for COPD patients, we constructed a decision analytic model with two alternative decisions for the AD, *Do Not Intubate* ([DNI] i.e., no invasive mechanical ventilation) and *Full Code* (i.e., may use invasive mechanical ventilation if necessary) in the event of respiratory failure from a COPD exacerbation.

**TO:**

To inform the AD discussion for COPD patients, we developed a decision model for advanced directives that could accommodate a wide array of patient preferences. Decision analytic modeling is used for complex decision making in which there are competing treatments and prognoses. Treatment pathways and outcomes are represented explicitly, often using computer simulation, with probabilities based on published clinical studies. The ‘preferred’ or ‘recommended’ decision is that which maximizes the expected value of the outcome of interest, such as survival, quality of life or cost-effectiveness. Modeling is used to supplement clinical data in situations when the influential variables of the decision need to be discovered and when there is uncertainty about clinical inputs. A well-designed decision model can function as a virtual clinical trial, with the benefit of being able to change all the parameters individually or simultaneously to test the effect on outcomes and to discover the most influential variables.

**FROM:**

Our model follows patients with COPD who are having annual AD discussions (Figure 1).

**TO:**

Our model follows hypothetical patients with COPD who are having annual AD discussions (Figure 1).

And in the Discussion section we inserted:

“Future research will also explore eliciting the patient preferences that can be used by our model.”
Referee # 1
Reviewer’s report
“1. The paper is long, difficult to read and follow”

Author’s Response
We have edited the text to address this concern:

- METHODS SECTION

FROM:
Utilities
Utility is a preference-weighted, one-dimensional, generic quality of life measure on a scale of 0-1. We estimated COPD utilities based on reported estimates for chronic lung diseases including COPD and cystic fibrosis before and > 4 months after lung transplant. Chronic lung diseases overall confer a reported utility ranging from 0.65 (very severe; on waiting list for transplant) to 0.80 (undifferentiated by severity) (34). Correspondingly, we based our moderate COPD utility estimate on the midpoint of this range and varied this in sensitivity analyses. We calculated the utility of discharge to long-term ECF using the published methods by Torrance et al. (35) to calculate utilities from hypothetical time tradeoff scenarios. In these hypothetical scenarios patients were asked how much time in their current state of health they would tradeoff to avoid 1 month of complications from intubation. These utilities had negative values (corresponding to states worse than death) if the patient was willing to tradeoff large amounts of time alive to avoid 1 month of intubation and associated complications. For example, if a patient with severe COPD was willing to tradeoff 1 year of life in their current health to avoid 1 month long-term institutionalization, for that particular patient, long-term ECF would have an inferred utility of -7.98. The utility of complications from intubation was calculated using the same method as it could have a wide range of patient preferences that could influence AD decision making.

TO:
Utilities
Utility is a preference-weighted, generic, quality of life measure on a scale of 0-1. We estimated COPD utilities based on reported estimates for chronic lung diseases. (34) We calculated the utility of discharge to long-term ECF and the utility of ETT complications using time tradeoff scenarios in which hypothetical patients were asked how much time in their current state of health they would tradeoff to avoid 1 month of complications from intubation. (35) These utilities had negative values (corresponding to states worse than death) if the patient was willing to tradeoff large amounts of time alive to avoid 1 month of intubation and associated complications.
RESULTS SECTION
FROM:

Sensitivity Analyses
We varied each input to the model across its plausible range to determine whether our results were robust (i.e., whether the recommended AD changed to Full Code and whether the difference in QALY changed substantially), performing separate sensitivity analyses for mild, moderate and severe COPD (Figures 2A-C). To focus our attention on model robustness, we first limited these analyses to patients who were unwilling to trade off any time alive to avoid intubation or long-term institutionalization. The mild COPD scenario (Figure 2A) yielded the most robust inferences for decision making. All except one of the probability ranges included 0, indicating that plausible range variation rarely changed the recommended AD. The moderate COPD scenario (Figure 2B) yielded less robust results, with wider variations in the QALY difference between Full Code and DNI. When the probability of having a complication from ETT increased, DNI became the recommended directive ($\geq 0.74$, DNI favored). The severe COPD scenario yielded the least robust inferences for decision making when patients did not have strong preferences against complications of intubation (i.e., were unwilling to trade off time alive to avoid intubation), as these narrow ranges included 0 for two variables. Non-preference variables that led to DNI being favored were an increase in the probability of ETT complications ($\geq 0.617$, DNI favored), and a decrease in the probability of failing NIMV when severely ill (i.e., higher likelihood of survival with just NIMV treatment; $\leq 0.14$ DNI favored). However, it is important to note that the severe COPD scenario yielded the most robust inferences for decision making when patients did have strong preferences against ETT complications (Full Code always favored in sensitivity analyses).

TO:

Sensitivity Analyses
We varied each input to the model across its plausible range to determine whether our results were robust (i.e., whether the recommended AD changed to Full Code and whether the difference in QALY changed substantially), (Figures 2A-C). We first limited these analyses to patients who were unwilling to trade off any time alive to avoid intubation or long-term institutionalization. The mild COPD scenario (Figure 2A) yielded the most robust inferences for decision making. All except one of the probability ranges included 0, indicating that plausible range variation rarely changed the recommended AD. The severe COPD scenario yielded the least robust inferences for decision making. Variables that led to DNI being favored were an increase in the probability of ETT complications ($\geq 0.617$, DNI favored), and a decrease in the probability of failing NIMV when severely ill (i.e., higher likelihood of survival with just NIMV treatment; $\leq 0.14$ DNI favored).

FROM:

Patients not willing to tradeoff time alive to avoid intubation
For patients who did not have a strong preference against complications of intubation, Full Code was recommended when compared to DNI regardless of COPD severity. However, the magnitude of recommendation decreased as the severity of baseline COPD increased. For patients with mild COPD, endorsing a Full Code AD increased quality-adjusted life years (QALYs) from 19.60 to 20.34 QALYs, a difference of 0.74 QALYs. For patients with moderate COPD, endorsing a Full Code AD increased
QALYs from 6.04 QALYs to 6.4 QALYs, a difference of 0.34 QALYs. For patients with severe COPD, endorsing a *Full Code* AD continued to increase QALYs albeit by a smaller amount (from 1.42 QALYs to 1.55 QALYs, a difference of 0.13 QALYs).

**TO:**

**Patients not willing to tradeoff time alive to avoid intubation**

For patients who did not have a strong preference against complications of intubation (i.e., were not willing to give up life expectancy to avoid complications of intubation), *Full Code* was recommended when compared to *DNI* regardless of COPD severity. However, the strength of the recommendation to be *Full Code* decreased as the severity of baseline COPD increased: for patients with mild COPD the increase in QALYs for choosing *Full Code* instead of *DNI* was 0.74 QALYs, whereas for patients with severe COPD the increase in QALYs for choosing *Full Code* instead of *DNI* was 0.13 QALYs.

**FROM:**

**Patients willing to tradeoff time alive to avoid intubation**

For patients who had a strong preference against complications of intubation (i.e., they were willing to tradeoff some time alive in order to avoid it), *DNI* was often recommended when compared to *Full Code*, particularly as the severity of COPD increased. For patients with mild COPD, *DNI* only became the recommended directive when the patient’s preference against intubation was extremely strong (willing to trade off ≥ 1 year to avoid 1 month of complications of intubation) (Figure 3A). For patients with moderate COPD, *DNI* became the recommended directive when patients were willing to trade off ≥ 6 months of time alive in order to avoid 1 month of complications of intubation, or when patients were willing to tradeoff ≥ 1 year of life expectancy in order to avoid 1 month of long-term institutionalization (Figure 3B). For patients with severe COPD, *DNI* was always the recommended AD unless a patient had only mild preferences against complications of intubation or long-term institutionalization (willing to tradeoff <3 weeks of time alive to avoid 1 month of complications of intubation and/or willing to trade off < 2 months of life expectancy in order to avoid long-term institutionalization) (Figure 3C).

**TO:**

**Patients willing to tradeoff time alive to avoid intubation**

For patients who had a strong preference against complications of intubation *DNI* was recommended compared to *Full Code*, particularly as COPD severity increased. For patients with mild COPD, *DNI* became the recommended directive when a patient was willing to trade off ≥ 1 year to avoid 1 month of complications of intubation (Figure 3A). For patients with severe COPD, *DNI* was always the recommended AD, unless a patient was only willing to tradeoff <3 weeks of time alive to avoid 1 month of complications of intubation and/or willing to tradeoff < 2 months of life expectancy in order to avoid long-term institutionalization (Figure 3C).

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2. “The methods are obscure and complicated for the reader (there are too much parts to be improved in clarity and I think is useless to discuss in details)”
**Author’s Response**
Please see answer to #1 (above) for the Methods section.

3. “It is not clear the final practical implication of these results”

**Author’s Response**
We have edited the Discussion section to address this concern:

**FROM:**
In summary, our model is one step towards informing AD decisions for patients with COPD and their clinicians, and will inform the development of decision aids and clinical decision supports to increase preference-congruent care. We have identified the need for clinical research on the probability of ETT complications and for elicitation of patient preferences as the most influential variables for AD decision-making in patients with COPD.

**TO:**

- **CONCLUSION**
In summary, our model estimates both the survival from alternate advance directives as well as the resulting quality of life based on individual patient preferences. We believe that making our model available to clinicians in the form of a decision aid will better inform AD shared decision making and is one step towards increasing preference-congruent care at the end of life.

“4. The figures are complicated and unclear”

Changes to legends for all three figures were made. Figures 2 and 3 were modified as well. The changes are easier to see with track changes within the document.

Changes to **Figure 1** were made in the legend

**FROM:**

Figure 1. The advance directives decision model. The square node at the left of the diagram is a “choose” node, representing the choice of endorsing a DNI versus Full Code AD. The circles at the origin of each branch are chance nodes, representing events that may or may not happen with a specified probability. The three base case analyses explore different scenarios regarding the severity of underlying COPD. Consequently, the probability of respiratory exacerbation in one year and the probability that the exacerbation is severe (severely ill), varied; all other probabilities were kept constant. After being admitted to the hospital with an exacerbation patients could be admitted to either the intensive care unit (ICU) or a regular ward (Ward), with non-ventilatory treatment (no NIMV) only offered on the Ward and ETT only in the ICU. Patients who failed mechanical ventilation patients could opt for no further treatment, (Comfort Measures Only; “CMO”). Complications of NIMV was defined as inability to wean from ventilator. Complications of ETT include failure to wean from ventilator in addition to end organ damage, such as infection, while on the ventilator.
The triangles at the end of each path represent the health effects associated with the full sequence of events in the path (Terminal Node). Paths end in death; discharge to either extended care facility for a short term or a long-term; or discharge to home.

* ECF discharge is either permanent institutionalization in an ECF (long-term ECF), or temporary institutionalization in an ECF followed by return to home (short-term ECF). Discharge to long-term ECF occurred only in the pathways where there were complications of mechanical ventilation or in patients who survived CMO.

TO:
Figure 1. The advance directives decision model. The square node at the left of the diagram is a “choose” node, representing the choice of endorsing a DNI vs. Full Code AD. The circles at the origin of each branch are chance nodes, representing events that may or may not happen with a specified probability. After being admitted to the hospital with an exacerbation patients could be admitted to either the intensive care unit (ICU) or a regular ward (Ward), with non-ventilatory treatment (no NIMV) only offered on the Ward and ETT only in the ICU. Patients who failed mechanical ventilation could opt for no further treatment. (Comfort Measures Only; “CMO”). The triangles at the end of each path (the ‘terminal node’) represent the health effects associated with the full sequence of events in the path Paths end in death; discharge to either extended care facility for a short term or a long-term; or discharge to home.

* ECF discharge is either permanent institutionalization in an ECF (long-term ECF), or temporary institutionalization in an ECF followed by return to home (short-term ECF). Discharge to long-term ECF occurred only in the pathways where there were complications of mechanical ventilation or in patients who survived CMO.

The figures have been changed to outline only the most influential variables and the implication of the vertical line at QALY 0.0 has been explained within the diagram.

The figures have been changed to uniform color (instead of different shading of the bars) and the full name of the variable (rather than p_ and u_ which represented probability of and utility of). The figures now also include a clear demarcation of when the variable causes a change in preferred directive from Full Code to DNI (inserted text box with this in the figure).

The legend has been modified:

FROM:
Figure 2. Tornado Diagrams. Results of one way sensitivity analyses are illustrated as tornado diagrams with the horizontal bars representing the incremental change in QALYs for Full Code compared to DNI advance directive. The widest bars represent the variables that the model is most sensitive to because changes in their parameter estimates result in large changes in QALY. Variables that cross the 0 mark indicate a change in the recommended AD from Full Code to DNI. Three separate graphs correspond to the three alternative scenarios for COPD severity in our base case analyses. (A, Mild COPD; B, Moderate COPD; C, Severe COPD).

For the mild COPD scenario (Figure 2A), there was no change in the recommended directive.
For the moderate COPD scenario (Figure 2B), *DNI* became the recommended directive when the probability of having a complication from ETT increased.

For the severe COPD scenario (Figure 2C), *DNI* became the recommended directive when the probability of having a complication from ETT increased; and when the probability of failing NIMV decreased.

\[ p_\text{=} \text{probability of}; \ u_\text{=} \text{utility of}; \ ETT = \text{Invasive mechanical ventilation via endotracheal intubation}; \ NIMV = \text{Noninvasive mechanical ventilation}; \ ECF = \text{Extended Care Facility}; \ CMO = \text{Comfort Measures Only}; \ DNI = \text{Do Not Intubate}; \ ICU = \text{Intensive Care Unit}. \]

* used “Life expectancy adjuster” variable to ensure that all life expectancies were varied in parallel when life expectancy was changed. (range used for sensitivity analysis was 0.56 – 2.78)

**TO:**

**Figure 2. Tornado Diagrams.** Three separate graphs correspond to the three alternative scenarios for COPD severity in our base case analyses. (a., Mild COPD; b., Moderate COPD; c., Severe COPD).

Results of one way sensitivity analyses are illustrated as tornado diagrams with the horizontal bars representing the incremental change in QALYs for *Full Code* compared to *DNI* advance directive. The widest bars represent the variables that the model is most sensitive to because changes in their parameter estimates result in large changes in QALY. Variables that cross the 0 mark indicate a change in the recommended AD from *Full Code* to *DNI*.

For the mild COPD scenario (Figure 2a), there is no change in the recommended directive when parameter estimates for the model variables are changed.

For the moderate COPD scenario (Figure 2b), *DNI* becomes the recommended directive when the probability of having a complication from ETT increases.

For the severe COPD scenario (Figure 2c), *DNI* becomes the recommended directive when the probability of having a complication from ETT increases; and when the probability of failing NIMV decreases.

\[ p_\text{=} \text{probability of}; \ u_\text{=} \text{utility of}; \ ETT = \text{Invasive mechanical ventilation via endotracheal intubation}; \ NIMV = \text{Noninvasive mechanical ventilation}; \ ECF = \text{Extended Care Facility}; \ CMO = \text{Comfort Measures Only}; \ DNI = \text{Do Not Intubate}; \ ICU = \text{Intensive Care Unit}. \]

**FROM:**

**Figure 3. Sensitivity Analyses of the utility of discharge to long-term ECF and of the utility of having a complication from intubation.**

Results of two way sensitivity analyses are illustrated as tables with increasing willingness to tradeoff time from life expectancy in order to avoid one month of discharge to long-term ECF; and to avoid one month of having complications from intubation. The shaded regions are utilities for which the recommended directive is *DNI*. Utilities were calculated from hypothetical time tradeoff scenarios using the published methods by Torrance et al. (34) (61). In these hypothetical scenarios patients were asked how much time in their current state of health they would tradeoff to avoid 1 month complications from intubation; or discharge to long-term ECF. These utilities had negative values (corresponding to states
worse than death) if the patient was willing to tradeoff large amounts of time alive to avoid 1 month of complications from intubation. The numbers in brackets represent calculated utilities.

Three separate figures correspond to the three alternative scenarios for COPD severity in our base case analyses. (A, Severe COPD; B, Moderate COPD; C, Mild COPD).

For the mild COPD scenario (Figure 3A), DNI became the recommended directive only when the patient was willing to tradeoff more than one year of life expectancy in order to avoid complications of intubation.

For the moderate COPD scenario (Figure 3B), DNI became the recommended directive when the patient was willing to tradeoff more than 6 months of life expectancy in order to avoid complications of intubation. DNI also became the recommended directive when the patient was willing to tradeoff more than 1 year of life expectancy in order to avoid long-term ECF. When taking both patient preferences into account, if the patient was willing to tradeoff more than 2 months of life expectancy in order to avoid complications of intubation, and also more than 2 months of life expectancy in order to avoid long-term ECF, DNI was the recommended directive.

For the severe COPD scenario (Figure 3C), DNI became the recommended directive when the patient was willing to tradeoff more than 1 month of life expectancy in order to avoid complications of intubation. DNI also became the recommended directive when the patient was willing to tradeoff more than 2 months of life expectancy in order to avoid long-term ECF. When taking both patient preferences into account, if the patient was willing to tradeoff more than 1 week of life expectancy in order to avoid complications of intubation, and also more than 1 month of life expectancy in order to avoid long-term ECF, DNI was the recommended directive.

TO:

Figure 3. Sensitivity Analyses of the utility of discharge to long-term ECF and of the utility of having a complication from intubation.

Results of two way sensitivity analyses are illustrated as tables with increasing willingness to tradeoff time from life expectancy in order to avoid discharge to long-term ECF; and to avoid having complications from intubation. The shaded regions are utilities for which the recommended directive is DNI. Utilities have negative values (corresponding to states worse than death) if the patient is willing to tradeoff large amounts of time alive to avoid complications from intubation. The numbers in brackets represent the calculated utilities.

Three separate figures correspond to the effect of preferences on the AD decision depending on whether patients have different severities of baseline COPD. (a., Severe COPD; b., Moderate COPD; c., Mild COPD)

For patients with mild COPD (Figure 3a), DNI becomes the recommended directive only when the patient is willing to tradeoff more than one year of life expectancy in order to avoid complications of intubation.

For patients with moderate COPD (Figure 3c), DNI becomes the recommended directive when the patient is willing to tradeoff more than 6 months of life expectancy in order to avoid complications of intubation.
DNI also becomes the recommended directive when the patient is willing to tradeoff more than 1 year of life expectancy in order to avoid long-term ECF. When taking both patient preferences into account, if the patient is willing to tradeoff more than 2 months of life expectancy in order to avoid complications of intubation and discharge to long-term ECF, DNI becomes the recommended directive.

For patients with severe COPD (Figure 3c), DNI becomes the recommended directive when the patient is willing to tradeoff more than 1 month of life expectancy in order to avoid complications of intubation. DNI also becomes the recommended directive when the patient is willing to tradeoff more than 2 months of life expectancy in order to avoid long-term ECF. When taking both patient preferences into account, if the patient is willing to tradeoff more than 1 week of life expectancy in order to avoid complications of intubation and discharge to long-term ECF, DNI becomes the recommended directive.

5. “The authors have inserted too much references”
Most of our references are due to the table that outlines the evidence base for the parameter estimates used in the model. We have moved the table (exceeded the two page limit) to an appendix that can be viewed by interested readers, which has decreased the number of references from 62 to 44.

6. “The crucial point is: who is the candidate to submit this type of questionnaire? The difficult prognosis, the correct timing during the unclear time course, previous clinical and care experiences, rehabilitation opportunities, the real risk of death are disturbing factors which did not allow a generalization of questions, habits and answers on this field”

We have modified the manuscript in the Discussion section to address these concerns:

FROM:

Although there was insufficient data to inform estimates for some variables requiring us to rely on a single study or on expert opinion, the influential variables on sensitivity analysis were not derived by expert opinion. The probability of ETT complications, however, was an influential variable for which only one study was available (41), because most studies do not distinguish between mortality from ETT and complications from ETT that lead to mortality. (41)We have thus identified an important variable to focus future clinical research in the intensive care unit. Increased data on the probability of ETT complications will improve advance directive decision making by allowing quality of life to be discussed in the event of survival after intubation. In addition, the preference-specific variables (e.g., willingness to trade off time alive to avoid intubation), were not derived from the literature. We argue that these variables are more informative if patient-specific rather than based on cohort studies from the literature. Patient-specific preferences will be obtained in the future by coupling the model to a decision aid that elicits patient-preferences (e.g., preferences about health states) and will allow for individually tailored advance directive recommendations.

TO:
Another important limitation of our model is that it does not use state transitions, and therefore is not able to assess the influence of multiple respiratory exacerbations within one year. Patients who have multiple exacerbations have increasing severity exacerbations and poorer outcomes than is reflected in the model \{[885 Donaldson,G.C. 2002; 898 Seemungal,T.A. 1998]\}. Additionally, we assumed that the utility of discharge home after a COPD exacerbation, and LE, was the same as the utility and LE before COPD exacerbation. The literature suggests that some patients who are discharged home do not return to normal quality of life immediately, and that health related quality of life suffers for some time after the acute symptoms have resolved \{[898 Seemungal,T.A. 1998; 942 Cote,C.G. 2007]\}. Future work includes evolving the decision tree into a Markov state transition model that can represent the clinical course of severe COPD with greater fidelity; and incorporating the model into a decision aid using patient preference to support shared decision making. Although we believe that informing all COPD patients about alternate treatment options in the event of severe respiratory exacerbations, the ideal timing of this discussion needs to be established (e.g., after deterioration in PFTs are noted in a patient with severe COPD). Appropriate psychiatric counseling may also need to be made available in the event of any distress caused by the discussion of end of life scenarios, and future work on a decision aid will assess patient’s reactions to this discussion.

7. “No data are presented for COPD previous history, H admissions, ADL previous admission to study, level of depression, anxiety, use of oxygen or NIV, socio-economical status, the religion, the presence of chronic respiratory failure, the types of support that they will eventually have in case of disease worsening (i.e. living close to other family members, living alone, living in the countryside vs the city), the level of education of patients”

We have modified the manuscript in the Discussion section to address these concerns:

FROM:

We used COPD exacerbations as the cause of respiratory failure in order to focus on a specific and common scenario requiring decision making. Using our results the clinician may initiate an AD discussion that is disease-specific for COPD patients with a focus on patient preferences about long-term outcomes of treatments such as the potential for long-term institutionalization. Other patient-specific factors, such as comorbidities or prior mechanical ventilation outcomes, may influence the probability of complications and change the recommended AD decision for individual patients, and should be explored in future clinical research.

TO:

We chose COPD-related respiratory failure in order to focus on a specific and common scenario requiring decision making. Using our results a clinician can compare and contrast prognoses with different AD choices. It is our hope that this will facilitate clinicians to initiate AD discussion with their COPD patients, incorporating their individual preferences (e.g., long-term institutionalization). Other patient-specific factors, such as physical and mental comorbidities, prior mechanical ventilation outcomes, prior
admissions, baseline functional status (ADLs) and home support, may influence the probability of complications and change the recommended AD decision for individual patients, and future clinical research should explore their relative importance and their feasibility for incorporation into decision supports. Future research may also explore further developing tools to elicit the patient preferences identified by our model.

8. “The communication of end of life care may be also influenced by the emotional and psychological status, like anxiety and depression”

please see the response to # 7.

9. “Preferences under primary care physician or respiratory physicians may also change”

We have addressed this concern in the Discussion section:

FROM:
Another important limitation of our model is that it does not use state transitions, and therefore is not able to assess the influence of multiple respiratory exacerbations within one year. Patients who have multiple exacerbations have increasing severity exacerbations and poorer outcomes than is reflected in the model (42,43). Additionally, we assumed that the utility of discharge home after a COPD exacerbation, and LE, was the same as the utility and LE before COPD exacerbation. The literature suggests that some patients who are discharged home do not return to normal quality of life immediately, and that health related quality of life suffers for some time after the acute symptoms have resolved (43,44). Future work includes evolving the decision tree into a Markov state transition model that can represent the clinical course of severe COPD with greater fidelity; and incorporating the model into a decision aid using patient preference to support shared decision making.

TO:
Another important limitation of our model is that it does not use state transitions, and therefore is not able to assess the influence of multiple respiratory exacerbations within one year. Patients who have multiple exacerbations have increasing severity exacerbations and poorer outcomes than is reflected in the model (42,43). Additionally, we assumed that the utility of discharge home after a COPD exacerbation, and LE, was the same as the utility and LE before COPD exacerbation. The literature suggests that some patients who are discharged home do not return to normal quality of life immediately, and that health related quality of life suffers for some time after the acute symptoms have resolved (43,44). Future work includes evolving the decision tree into a Markov state transition model that can represent the clinical course of severe COPD with greater fidelity; and incorporating the model into a decision aid using patient preference to support shared decision making. Future work may also include gathering more knowledge about a wide variety of important domains, such as the effect of clinician’s specialty on the AD decisions, the influence of patient-specific factors such as gender, religion, cultural background, surrogate
involvement and living situation (i.e., what resources the patient has to assist with home care); and the patient’s reactions to the probabilities given by the model.

10. “No data on structured follow-up proposed to patients as dedicated office, tele-support, educational programs, continuity of care, access to drugs and home care.”

Please see the response to # 11

11. No data on access to rehabilitation programs
We have clarified within the text that short term ECF indicates rehabilitation:

**FROM:**
Long-term outcomes of treatment include permanent institutionalization in an extended care facility (long-term ECF), temporary institutionalization followed by return to home (short-term ECF), or discharge to home, and were dependent on the baseline severity of COPD exacerbation and preceding short-term outcomes

**TO:**
Long-term outcomes of treatment include permanent institutionalization in an extended care facility (long-term ECF), temporary institutionalization for rehabilitation followed by return to home (short-term ECF), or discharge to home, and were dependent on the baseline severity of COPD exacerbation and preceding short-term outcomes

12. No data on different clinical phenotypes
Please see the response to # 7.

13. No data on different baseline spiritual and religious preferences
Please see the response to # 9.

14. No discussion about media influence on patients
Please see the response to # 9.

15. “No data on role of caregiver and family on patient’s feeling and hope for the future”
Please see the response to # 9.

16. “Another limitation may be the fact that questionnaire describes only a perceptions rather than real assistance or care”
Please see the response to # 3.