Author's response to reviews

Title: Predictors of pneumococcal vaccination among older adults with pneumonia: findings from the Community Acquired Pneumonia Impact Study

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Author's response to reviews: see over
The authors would like to thank the three reviewers and the Associate Editor for their thoughtful and detailed review of this manuscript. As requested, we have provided below a point-by-point response to each of the issues raised.

Referee 1
Reviewer's report
Title: Predictors of pneumococcal vaccination among older adults with pneumonia: findings from the Community Acquired Pneumonia Impact Study
Version: 1 Date: 12 April 2010
Reviewer: Catherine A. Lexau
Reviewer's report:
Major Compulsory Revisions

(1) Use of this particular self-reported measure presents a major methodological problem in this analysis, particularly for persons in these age groups. Macdonald et al. (1999) found the specificity of self-report of pneumococcal vaccine to be 0.53 for patients over age 65 from a Veterans Affairs medical center and 0.76 for managed care organization patients in the same age group. In the latter group it was determined that false reports of vaccination were more likely when the vaccine was given more than 2 years prior to the self-report. It is true that self-report of pneumococcal vaccination is a measure used to monitor population uptake of this vaccine, for example, in the U.S. Behavioral Risk Factor Surveillance System. However, in this assessment, the goal was to identify factors predictive of pneumococcal vaccination. With this high likelihood of misclassification of the outcome, the validity of the study is questionable. Perhaps some other validation of the outcome (pneumococcal vaccination) was undertaken, or other literature supports use of this self-reported measure, but this should be addressed. Mac Donald, R., L. Baken, et al. (1999). "Validation of self-report of influenza and pneumococcal vaccine status in elderly outpatients." American Journal of Preventive Medicine 16(3): 173-177.

Response: Information regarding pneumococcal vaccination status was collected during telephone interviews with community-dwelling older adults with clinically diagnosed CAP who were able to provide informed consent. We acknowledged self-reporting of immunization status as a limitation of the study but do not believe that this is a fatal flaw. The literature would suggest that the sensitivity of self reported pneumococcal vaccination status is very good but there is more variability with reported specificity. In contrast to the 1999 MacDonald et al. findings mentioned by the reviewer, a study published in 2007 by Mangtani P et al. that included seniors with clinically diagnosed CAP (more similar to our study population) had a specificity of 0.87 for self reported pneumococcal vaccination (Mangtani P, et al. Validation of influenza and pneumococcal vaccine status in adults based on self-report. Epidemiology and Infection 2007; 135:139-43.). One potential reason for the variability in specificity is the validity of the source of the comparison data (i.e. medical charts). This is particularly important in Ontario where older adults have easy access to community immunization clinics outside family physician practices (notices regarding immunization would not be sent to family physicians). It has also been estimated that 1.2 million (14% of Ontario residents) are without a family physician (Ontario
Medical Association, 2005) which further brings into question the use of medical charts to validate immunization status. The inaccuracy of using medical charts could therefore account for some of the variability in specificity noted in the literature.

The limitations section was expanded as follows to address this issue: “Self-reported immunization status is another potential limitation. The literature would suggest that the sensitivity of self reported pneumococcal vaccination status is very good but there is more variability with reported specificity. However, one potential reason for the variability in specificity is the validity of the source of the comparison data (i.e. medical charts). This is particularly important in Ontario where a relatively high percentage of the population are without a family physician and where older adults have easy access to community immunization clinics outside family physician practices (notices regarding immunization would not be sent to family physicians). The inaccuracy of using medical charts could therefore account for some of the variability in specificity noted in the literature.”

Minor Essential Revisions

(2) Even though they were standardized, the use of self-reported assessment measures may have led to uncontrolled confounding of the reported associations. For example, poor memory of pneumococcal vaccination might occur more often among participants who also had poor or inaccurate recall of other factors such as comorbid diseases. Somehow this should be addressed, at least as a possible weakness of the study.

Response: There are two issues related to recall. The first relates to potentially inaccurate recall of "exposures" such as comorbidities, etc. These recall problems (which likely exist in varying degrees for all people and tend to be a potential limitation for most studies) are not systematic but tend to represent random error which will likely cancel each other out in the two groups (i.e. are the same in both the immunized and not immunized groups). For recall bias to occur, those who were immunized would have to recall their other exposures differently than those who were not immunized. Recall bias is less likely to occur in this study, than in studies with more serious outcomes, such as cancer, where the participants are more likely to "search" for potential causes for their cancer (and therefore remember exposures differently) than those without cancer. The limitation section was expanded to include the following. "Although we expect the accuracy of the information collected from study participants to be very good, based on the use of reliable and valid instruments, some degree of random error should be expected in studies that collect self reported data retrospectively. However, we don't suspect that recall bias is a weakness of this study.”

(3) These are details that should be included in the methods section: full spelling and/or citations should be given for assessment tools (SF8, Barthel Index, Lawton). Dates (specific onths/years) of data collection should be included.

Response: Full spelling has been provided in the methods section for the SF-8, Barthel, and Lawton instruments as follows:

...using the Short-Form-8 Health Survey (SF-8) to collect information on ...; functional status (measured using the 10-item Modified Barthel Index which includes grooming; instrumental
activities of daily living scale (measured using the 8-item Instrumental Activities of Daily Living Scale developed Lawton which includes items...
The sentence "Data collection ended March 2004." was added to this section. It was stated earlier in the manuscript that participants were recruited over a 15 month period and that they were contacted for interview 4 weeks after their recruitment.

(4) The extent to which patients agreed to participate at the point of recruitment is unclear. Did they agree to be contacted for a phone interview? What was the total number recruited, and were there any recruited who did not complete a phone interview? Were any reasons for drop-out available to investigators?

Response: All x-ray technicians from all the community and hospital radiology centres were formally trained to recruit participants and used the following criteria in their recruitment: x-ray being taken to verify/rule out CAP; 60 years of age and older; able to speak English; ability to obtain informed consent. Participants provided their consent to allow their contact information to be released to the study researchers so they could be contacted for a telephone interview and to contact their family physician to obtain the results of their chest x-ray. The x-ray technicians were asked to document the number of eligible people who declined participation and the reason for declining. A total of 44 people declined participation. The reason for declining was that the patients simply did not want to participate. Of those who agreed to participate, 86% (195) completed the telephone interview. Of these 195, 185 provided information about their pneumococcal vaccination status. The above information has been clarified in the methods and results sections as appropriate.

Discretionary Revisions:
(5) Most of the quality of life and social support measures assess the participant’s current status; but the outcome of interest is past pneumococcal vaccination. I think it would be best to justify this or else describe this as a possible limitation of the study.

Response: Actually most information collected was for the time period before they got CAP with some social support questions being framed in the last 6 months. The issue of recall related to pneumococcal vaccination was addressed above.

(6) It would be better to include more specifics in methods of age eligibility (assume 60+ years) and whether only community-living adults were included. (Does CAP mean those living in long term care facilities/nursing homes were excluded?)

Response: This information has been clarified in the Methods (Recruitment) section....Eligibility criteria included being clinically diagnosed with CAP by a family or emergency room physician, being 60 years of age or older, living in the community (Brant County), presenting for a chest x-ray at one of the community or hospital radiology centres, speaking English, and obtaining informed consent. Exclusion criteria included: cognitive impairment and having hospital or nursing home acquired pneumonia.
(7) It appears to me that type I error was possible in the analysis. Perhaps it would be good to review the number of associations tested, and determine a means of limiting this possibility, if appropriate.

Response: We agree with the reviewer that our sample size was not that large. However, we performed bivariate analyses to eliminate nonsignificant predictors first, then we performed the logistic regression on a smaller number of potential predictors. We kept only 7 significant predictors in our final model that included approximately 100 outcome events which fulfills the requirements (1 variable for 10 outcome events) for having reliable parameter estimates. In the limitation section we expanded on this issue that our wide confidence intervals are due to small sample size and relatively large number of predictors.

(8) The discussion would be strengthened by consideration of the meaning of the multi-variable findings as a group, and/or from the standpoint of confounding. Although all factors in Table 2 were judged as contributing to the best model, I felt that an overall message concerning these various risk/protective factors was missing. I would be interested in the authors’ assessment of why the influenza vaccine-pneumococcal vaccine association was stronger in the adjusted vs. univariate analysis.

Response: A footnote is provided in Table 2 to help with the interpretation of adjusted odds ratios. In response to the change in odds ratio (unadjusted value vs adjusted value), conducting a multivariable analysis that includes several predictor variables increases the demand on sample size. The effect of this can be observed from the wider confidence intervals and the correspondingly less precise odds ratio. These confidence intervals also overlap.

(9) Some paragraphs describing the possible reason for each individual finding included in the final model also seemed somewhat speculative, especially those covering social support, pain and religious faith.

Response: We agree that some comments are speculative but acknowledged them as being so.
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Response: Reviewer 2 did not have any "Major Compulsory Revisions" or "Minor Essential Revisions"

Discretionary Revisions (which the author can choose to ignore)
1.- Abstract (third line): I suggest change "prevalent" for "incident"

Response: We prefer to retain the word prevalent.

2. Discussion: Similarly with this study, a classical study by Zimmerman et al also found a strong association between receipt influenza and pneumococcal vaccination in elderly persons. I suggest that this concern could be commented in the Discussion and referenced (Zimmerman RK, Santibanez TA, Fine MA, et al. Barriers and facilitators of pneumococcal vaccination among the elderly. Vaccine 2003;2001:1510-17).

Response: This issue was commented on in the results section in terms of both the timing of vaccinations and a missed opportunity for pneumococcal vaccination.

3.- References: The references are quite good. However, the writing name of the journals should be revised because some are written as abbreviated name whereas other journals are written as complete name.

I suggest that reference 12 (Dear et al, Cochrane review 2003) and reference 15 (Moberley et al, Cochrane review 2008) could be unified in only one reference (the second basically is an update of the first).

Response: The references have now been revised to include abbreviated names.

4- Tables: I suggest to introduce the term "univariate analysis" in the title of Table 1. I believe that Table 1 is too long and it could be summarized.

Response: We prefer the current name for Table 1. This table is referred to in the text as showing the findings from the bivariate analysis of the variables to be included in the logistic regression analysis.

Reviewer's report
Title: Predictors of pneumococcal vaccination among older adults with pneumonia: findings from the Community Acquired Pneumonia Impact Study
Version: 1 Date: 21 April 2010
Reviewer: Kerry'Ann O'Grady
Reviewer's report:
This is a largely descriptive study that aimed to identify predictors of pneumococcal vaccination amongst older adults with clinically diagnosed CAP. It appears to be a sub-analysis of data collected from a larger study. Improving uptake of vaccine amongst older adults is an important public health goal. This paper may be useful to policy makers in the area of Canada from which the study population was derived. There are some limitations to the study that would preclude broad generalisations of the study findings to other populations. It is a very small sample size from which multiple analyses were performed. You are going to get “statistically significant results” by chance alone with these types of analyses, although the authors state they did consider whether something was theoretically plausible for it to be included in the model. The conclusions are also somewhat limited with respect to generalisability in that the data only reflect individuals with CAP, not the broader community. Predictors of vaccination amongst the elderly without “clinically diagnosed CAP” may be very different. Furthermore, there was no attempt to standardise the diagnosis of CAP in people included in the study, this can vary widely (more specific comments are below). The authors need to expand on the limitations section of the study as I do not think it sufficiently addresses the issues. My specific comments lead to a conclusion that this paper can be accepted for publication in this journal under the category of Minor

Essential Revisions.

1. Background, second paragraph, line 1. S. pneumoniae needs to be written in italics

Response: Now written as "Streptococcus Pneumoniae"

2. Background, 3rd paragraph: you need to specify whether the vaccine is publicly funded in Canada as this has a major impact on uptake

Response: This has been added as follows: In order to further understand PPV uptake in Canada, where the vaccine is publically funded, we explored...

3. Results: Paragraph 1. The authors must provide data on the number of people approached to enter the study, the number and % of those who consented and the number who completed the interview. This is essential as it enables a better picture of the representativeness of the study and whether some selection biases were operating. Some basic data comparing those who did and did not consent would be good. Furthermore, you need to present data on how many of these people had pneumonia confirmed by xray (albeit the known the limitations with this).

Response: Paragraph 1 has been expanded to address the question of numbers as follows: Forty-four potentially eligible patients refused to participate to consent to participate. Of those who initially agreed to participate, 86% completed the telephone interview. Of the 195 participants, 185 reported on their pneumococcal vaccination status. Of the 195 participants 95 had x-ray confirmed CAP – this was added to the results section “Sample Characteristics”. The limitation section has been expanded to include the following: The decision to use clinically diagnosed CAP versus x-ray confirmed CAP was based on there being no important differences in the characteristics or outcomes of those clinically diagnosed versus those with a positive chest x-ray;
the fact that a large percentage of physicians do not send their patients for chest x-rays; and to increase the sample size for this analysis.

4. Results, Paragraph 2. As mentioned previously this is an enormous amount of variables to add to a model with a very small sample size. You are going to need to expand on this in the discussion with respect to limitations.

Response: The limitations section has been expanded to include “Sample size was also a limitation of this study, resulting in large confidence intervals. In defense of this, however, we restricted our analyses to only include meaningful variables that were chosen a priori and our multivariate modeling fulfilled the requirement (1 variable for 10 outcome events) for having reliable parameter estimates.” In the methods section we also stated that these variables were selected a priori based on the literature and clinical experience.

5. Results, the tables: they are very cumbersome to wade through in the current format (ie with the double line spacing). This needs to be addressed in the proofs.

Response: The tables have been single spaced.

6. Discussion. As above, my major concern is the issue generalisability and the potential for this to be viewed as “data mining” exercise. The limitations of the study need to be more appropriately addressed, ie in the context of what they mean for the study findings.

Response: One of the original study objectives was to determine predictors of pneumococcal immunization among older adults with CAP. An attempt was made to recruit all older adults from an entire community over a 15 month time frame who were clinically diagnosed by a family physician as having CAP and who were sent for a confirmatory chest x-ray. All variables selected as potential predictors of immunization status were selected a priori. Add to this, the relatively high percentage of older adults who agreed to participate in the study - this contrary to the notion of this being a data mining exercise.

Associate Editor comments:

1. The study is conducted among patients with CAP. The choice of the study population is justified by existing evidence that the PPV may reduce the severity of CAP among older adults. In this study, patients with CAP who were vaccinated were older, had more comorbidities and more disabilities than non-vaccinated patients. Although the study is conducted in patients with CAP, the conclusion and interpretation of results tend to be stated in terms of the general elderly population. Patients without CAP may be much different from those with CAP and were not considered in this study. The authors should clarify how the findings from this study could inform future pneumococcal immunization strategies in Canada by identifying those individuals who are least likely to receive the PPV? In other terms, how a health policy maker should interpret the results of this study.
The conclusion section has been reworked as follows to address this issue: “In conclusion, this study identified a wide range of factors, including demographic (age), comorbidity (having at least one health condition; amount of bodily pain), quality of life (the extent that health problems limited usual activities), social support (frequency chatting or doing something with a friend) and lifestyle (recent influenza immunization; and the amount that spiritual values or religious faith played a role in life) to be associated with pneumococcal vaccination status among older adults with clinically diagnosed CAP. CAP is a relatively common infection among community-dwelling elderly. Although there are identified comorbidity risk factors for CAP, such as chronic lung disease, one of the most important is age with the “older” elderly being at highest risk. Because the risk of invasive pneumococcal disease increases in this group, for which there is excellent evidence that the vaccine is effective, from a health policy perspective this is indeed the group that should be targeted for pneumococcal immunization. The findings of this study, by helping to delineate the likelihood of receiving the vaccine, identify factors that need to be considered when targeting vaccine to the “low-uptake” elderly. Therefore, the findings from this study could inform future pneumococcal immunization strategies in Canada by identifying those individuals who are least likely to receive the PPV.”

2. Were patients with confirmed CAP identified? Clarify the reason why the study was not conducted among those?

Response: Yes, we were able to identify those with x-ray confirmed CAP. The decision to use clinically diagnosed CAP versus x-ray confirmed CAP was based on there being no important differences in the characteristics or outcomes of those clinically diagnosed versus those with a positive chest x-ray; the fact that a large percentage of physicians do not send their patients for chest x-rays; and to increase the sample size for this analysis. This issue is now included as one of the study's limitations.

3. Getting an influenza vaccine within the past year was the most important predictor of PPV among older adults. Another study has found that people get influenza vaccine and PPV at the same time. Have you verified this issue in this study?

Response: Although we collected information about whether or not participants received the influenza vaccine and the pneumococcal vaccine, we did not ask them if they received them at the same time. In Ontario Canada the general public has greater opportunity for receiving the influenza vaccine than the pneumococcal vaccine through influenza vaccination clinics that are regularly held in various communities such as the one where this study was conducted. These clinics are promoted in the mass media.

4. Abstract: some variables appear for the first time in the conclusion and are not defined in the abstract such as quality of life, social support and lifestyle?. Either mention these variables in the body of the abstract or adjust the conclusion.

Response: The "Data Collection" section within the Methods section clearly lists the various categories of variables (e.g. demographic, social support etc.) and provides examples of each (for example: "demographic characteristics (gender, age, marital status, living arrangements, cultural
background, level of education, household income, perceived level of social status, employment history); co-morbidities (e.g. allergies, asthma, chronic bronchitis, diabetes, emphysema, heart disease, cancer and liver disease); lifestyle (e.g. immunizations, having a family physician, smoking status, exposure to second hand smoke, alcohol consumption, ownership of pets, nutrition, spiritual values, overall happiness);” etc. Table 1 also reports the bivariate findings within the various categories of variables (e.g. demographic, social support etc.).

The conclusion section has been rewritten as follows to label these variables more clearly: In conclusion, this study identified a wide range of factors, including demographic (age), co-morbidity (having at least one health condition; amount of bodily pain), quality of life (the extent that health problems limited usual activities), social support (frequency chatting or doing something with a friend) and lifestyle (recent influenza immunization; and the amount that spiritual values or religious faith played a role in life) to be associated with pneumococcal vaccination status among older adults with clinically diagnosed CAP.

5. In the Background section, first paragraph, in the sentence ?Health outcomes related to CAP deteriorate with an increase in age?, say which health outcomes you mean.

Response: This has been rewritten as follows to be more clear: “CAP is a leading cause of hospital admissions and mortality in Canada [2,4,5] and with increasing age, there is a corresponding increase in morbidity and loss of independence for older adults [6,7].”

6. The statement: ?Seniors with cardiopulmonary disease, poor functional status (such as limitations with activities of daily living), weight loss or recent changes in weight are at increased risk for CAP?. These are risk factors for CAP and are not very relevant to this study since all study patients have CAP.

Response: The risk of CAP increases with age. Among those aged 65 years and older, cardiopulmonary disease, low weight, recent weight loss, and poor functional status have been identified as risks. Jackson ML, Nelson JC, Jackson LA. Risk factors for community-acquired pneumonia in immunocompetent seniors. JAGS 2009;57:882-888.

7. The Tables indicate that study patients are 60 years of age and older while from reading the text, we get the impression that study patients are 65 years or older. Clarify.

Response: This has been clarified in the document (both in the Abstract and Recruitment section of the Methods). The study recruited older adults aged 60+.

8. In data collection, define the following variables: living arrangements, cultural background, level of education, household income, perceived level of social status, employment history, immunizations (when), alcohol consumption, nutrition, spiritual values, overall happiness support (numbers and types of family relatives, friends, distance to these contacts, frequency of contact, involvement in social and religious networks.
Response: This section has been rewritten to provide additional information about the variables as follows:

**Data Collection**
The interviewer collected detailed information including: demographic characteristics (gender, age, marital status, living arrangements (i.e. number, ages and relationships of people living in the household; owning or renting; type of dwelling), cultural background (i.e. the ethnic or cultural group most identified as representing their heritage), level of education (categories from none to a university graduate degree), household income (total household income before taxes and deductions in $20k increments), perceived level of social status (as measured by the MacArthur Scale of Subjective Social Status), employment history (whether currently employed; main occupation when employed); co-morbidities (e.g. allergies, asthma, chronic bronchitis, diabetes, emphysema, heart disease, cancer and liver disease); lifestyle (e.g. immunizations (if ever received the influenza and pneumonia vaccines; and the timing either < 1 year ago; 1 to 2 years ago; more than 2 years ago), having a family physician, smoking status, exposure to second hand smoke, alcohol consumption (ever in the past 12 months), ownership of pets, nutrition (frequency skipping meals, number of servings of fruits, vegetables, milk products, meal replacements/supplements; difficulty chewing or swallowing; self perceived appetite), spiritual values (rating of how much spiritual values or religious faith plays a role in their life), overall happiness (rating from very unhappy to very happy)); quality of life (using the Short-Form-8 Health Survey (SF-8) to collect information on overall health, activity limitation because of health problems, difficulty doing usual daily activities because of physical health, amount of bodily pain, level of energy, limitations of social activities and activities due to personal or emotional problems); functional status (measured using the 10-item Modified Barthel Index which includes grooming, dressing, feeding oneself, transferring from one’s bed to a chair, bathing, toilet use, bladder control, bowel control, mobility, climbing stairs); instrumental activities of daily living scale (measured using the 8-item Instrumental Activities of Daily Living Scale developed Lawton which includes items on meal preparation, mobility beyond short distances, shopping, phone calling, doing laundry, doing household work or handymen work, taking one’s medication and money managing); and social support (numbers and types of family relatives, friends, distance to these contacts, frequency of contact, involvement in social and religious networks). Data collection ended March 2004.

9. In Data Analysis, first paragraph, add ?Crude? to odd ratios (ORs) and 95% confidence intervals.

Response: Rather than "crude", the word "unadjusted" was inserted before odds ratios...

10. In the statement, T?-tests were used to determine statistical significance is better stated as ?T?-tests were used to compare continuous variables between the vaccinated and non-vaccinated patients?.

Response: Change made.

11. In ?Logistic regression analysis was used to identify the best predictors..? delete ?best? and say how the final model was selected?
Response: The section was rewritten in greater detail and in a way to explain the use of "best" predictors as follows: A logistic regression analysis was used to identify the best predictors of pneumococcal vaccination status from those variables which had a statistically significant association in the above bivariate analyses or were considered by the investigators to be theoretically significant. A forward selection process was used whereby non-significant variables were removed from the model one at a time. The parameter estimates were reviewed at each step to assess whether the eliminated variable should be kept in the model to control for confounding.

12. The Cox and Snell (R²) and Nagelkerke (R²) statistics are also reported. Clarify what these statistics are for.

Response: The Cox and Snell and Nagelkerke R² provide estimates of the proportion of variance explained by the model. This information was provided in Table 2 (Cox & Snell R-square = .292; Nagelkerke R-square = .391 (i.e. between 29.2% and 39.1% of variance is explained by this model)). An explanation has now been added to the Data Analysis section of the Methods as follows: A rho-square value between 0.20 and 0.40 suggests a very good fit of the model. The Cox and Snell (R²) and Nagelkerke (R²) statistics are also reported as estimates of the proportion of variance explained by the final model.

13. In the Results section, give OR and 95% CI for key variables instead of a count of the significant variables. (one demographic characteristic; one co-morbidity; two lifestyle; one social support and two quality of life).

Response: The section was rewritten as it appears in the abstract as follows: The final logistic regression model included seven variables (Table 2): getting an influenza vaccine within the past year (OR 14.5, 95% CI 4.27 to 49.0); at least weekly contact with a friend (OR 3.97, 95% CI 1.71 to 9.24); having one or more co-morbidities/chronic conditions (OR 3.64, 95% CI 1.60 to 8.28); being 70 years of age or older (OR 2.56, 95% CI 1.21 to 5.40); having health problems that limited physical activities (OR 5.37, 95% CI 1.49 to 19.3); having little or no bodily pain (OR 2.90, 95% CI 1.25 to 6.73); and reporting having spiritual values or religious faith (OR 3.47, 95% CI 1.03 to 11.67). The final logistic regression model statistics are reported in Table 2.

14. In Discussion, results of the two variables: their health problems limited their usual activities a lot. were more likely to report having received the PPV? and older adults with mild to no bodily pain are more likely to have received the PPV? are somehow contradictory. Have you looked at interaction between these variables?

Response: Given that we did not anticipate any interactions a priori and the additional demand on sample size to examine interaction effects, we did not look at this interaction. Although our rationale for explaining these finding is somewhat speculative we didn't see these two findings as contradictory.
Editorial requests:

- Informed consent must be documented. Manuscripts may be rejected if the editorial office considers that the research has not been carried out within an ethical framework, e.g. if the severity of the experimental procedure is not justified by the value of the knowledge gained.

Response: Informed consent was obtained and as stated in the recruitment section, ethics approval was obtained from both McMaster University and the Brant Community Health Care System (formerly the Brantford General Hospital and the Paris Willett Hospital).

- The Tables should be presented more concisely. The references style should also be verified.

Response: The tables were single spaced and the references were written in abbreviated form.

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

Please also highlight (with 'tracked changes'/coloured/underlines/highlighted text) all changes made when revising the manuscript to make it easier for the Editors to give you a prompt decision on your manuscript.

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