PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Senior high cost healthcare users' resource utilization and outcomes: A protocol of a retrospective matched cohort study in Canada
AUTHORS	Muratov, Sergei; Lee, Justin; Holbrook, Anne; Paterson, Michael; Guertin, Jason; Mbuagbaw, Lawrence; Gomes, Tara; Khuu, Wayne; Pequeno, Priscila; Costa, Andrew P; Tarride, Jean-Eric

VERSION 1 – REVIEW

REVIEWER	Cilia Zayas University of Florida The College of Medicine Department of Health Outcomes and Policy United States
REVIEW RETURNED	14-Aug-2017

GENERAL COMMENTS	First, I would like to applaud the research team for focusing on the Senior high cost user population, a vulnerable yet often understudied group. Having said that, my recommendation is to not accept at this time, until a major revision of the referenced protocol is resubmitted for peer-review. My recommendation stems from the researchers proposed use of the Difference-in-Differences (DiD) design methodology. On page 10 the researchers state that it is appropriate to relax the DiD parallel trends assumption, "...as it is more important for causal inference, which is not a purpose of our study." I disagree with this statement, because for this study to provide unbiased marginal effects they must show how their design and respective data meets the DiD parallel trends assumption. The parallel trends assumption that underpins the DiD methodology is not just a requirement to establish causal inference. Estimates will be biased to the degree that the DiD parallel trends assumption is not met. If the researchers feel strongly that the DiD parallel trends assumption can appropriately relaxed, and study results still achieve unbiased estimates,historical studies should be provided with DiD references included to support the claim.

REVIEWER	Prof. Department of Primary Medical Care University Medical Center Hamburg-Eppendorf Germany Dr. Van den Bussche Hendrik
REVIEW RETURNED	16-Aug-2017

GENERAL COMMENTS	1. For a protocol of a research project, the manuscript in rather short, especially with regard to the chapters on a) Methods and Analysis and b) Analysis Plan (altogether 4,5 pages). The paper gives the impression of an application for funding developed a little further with minor changes to appear as a study protocol. Using the STROBE statement and the UCLH/UCL/RFH Biomedical Research Unit Guidelines as criteria for evaluation, one may conclude that the statistical methods are described in detail (see 2), but this is not the case for the handling of the variables, the data sets and the strategies for preventing bias. The variables of interest are only listed in the text, the datasets in a one-page appendix 1 and a (rather incomplete) list of “potential covariates” in appendix 3. It does by no way become clear which variables will be extracted from which databases and eventually grouped and/or transformed, or to which extent the 15 datasets will be matched (or not). For example, comorbidity will be captured as a patient characteristic but is remain unclear how this will be done on the basis of the “diagnostic information” available in at least 10 of the 15 datasets. On the other hand, it is not clear if morbidity will be restricted to the six special “ICES-derived cohorts” or not. Also, the manuscript does not contain any systematic description on the handling of confounders and effect modifiers. Although I recognize that it is quite complex – and pages consuming – exercise to define the handling of the datasets, the variables and the confounders, the actual version of the protocol deserves further elaboration in this respect. 2. As stated above, the description of the approaches to answer the three main research questions contains detailed information on the statistical and econometric methods. An econometrics expert should be found to review this aspect of the paper as econometry goes beyond the qualification of the reviewer. 3. The title of the paper deserves correction: a) the study is neither retrospective (nor prospective) but (one year) observational; b) the study is not a cohort-study but a case-control-study. 4. Independently of some critiques on the design of the study described above, I do not understand the rationale and I question the value of the study: In short: those 5% highest cost producing senior healthcare users incident in 2013 will be compared in a case control design with less cost producing users in a relation 1:3 (p. 8). Because of the incidence criterion the cases sample will consist mainly of elderly persons suffering from a very limited number of conditions (e.g. incident carcinomas with high cost therapies, sudden accidents and injuries requiring longer periods of hospitalization and/or rehabilitation and acute complications of chronic diseases (e.g. cerebral accidents on the basis of atherosclerosis). As matching will be done of the basis of age, sex and residence only, every individual in this very selective cases sample will be compared with only three controls (out of a population of several millions) who might belong – by definition – to a cost segment varying between 1% and 94% of all cost producing individuals. Therefore, the results will be difficult to generalize.

	This problem grows with the short observational period allowing conclusions for the first year only but none related to the more important question of persistence of HCU. Therefore, The question "whether HCU status is maintained versus an individual transitioning back to non-HCU" (p. 5) cannot be answered because of the short observation period. 5. The three main research question, as described in p. 7, are purely descriptive and associative but not led by hypotheses based on previous research. The number of important research questions as described in the introduction chapter is also higher than the three described, e. g. the question whether ACSC-condition do contribute to the hospital costs, the relationship between treatment costs and mortality, or the influence of physician payment models. A restriction of the number of questions might improve the quality, unless the duration and the budget of the project are unlimited (a note on the proposed duration is lacking!) 6. A study protocol should also state clearly which institution is responsible for which work package. 11 units are listed on p. 1 but any detail on responsibilities and division of labor is lacking. 7. The justifications of the study (p. 5, para 1 and 2; p 12: "Significance an policy implications") are vague and not very convincing. The authors themselves chose very unprecise terms, e.g. "to guide policies in Ontario", "help identifiy (..) interventions to possibly delay hospitalizations", or "prevent some of these patients from becoming new (persistent) HCU" etc. In sum, the paper needs a thorough revision in many senses.

REVIEWER	Robert C Amland Cerner Corporation, USA
REVIEW RETURNED	25-Sep-2017

GENERAL COMMENTS	Thank you for submitting this research prospectus. A major concern is measurement error on sepsis diagnosis codes. Sepsis is lethal, about 1 in 2 in-hospital deaths associated with sepsis in USA, and likely the most expensive condition for in-hospital care. Sepsis has been shown to be under-documented in electronic health record systems, which reduces diagnosis code assignment at discharge. How will this proposed study address this serious limitation with measurement error? Please refer to the following recent study, which reports sensitivity of sepsis using diagnosis code methodology is approximately 30%, which suggests 70% sepsis patients have a different diagnosis code at discharge. Several quality improvement studies in USA have corroborated this concern. Thank you for considering this substantial problem which impacts the statistical analysis methodology. Please refer to recent article: Rhee C, Dantes R, Epstein L, et al. Incidence and trends in US hospitals using clinical vs claims data, 2009-2014. JAMA. Published online September 13, 2017. Thank you again.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Cilia Zayas
Institution and Country: University of Florida, The College of Medicine, Department of Health Outcomes and Policy United States Please state any competing interests: None

Comment: First, I would like to applaud the research team for focusing on the Senior high cost user population, a vulnerable yet often understudied group. Having said that, my recommendation is to not accept at this time, until a major revision of the referenced protocol is resubmitted for peer-review. My recommendation stems from the researchers proposed use of the Difference-in-Differences (DiD) design methodology. On page 10 the researchers state that it is appropriate to relax the DiD parallel trends assumption, "...as it is more important for causal inference, which is not a purpose of our study." I disagree with this statement, because for this study to provide unbiased marginal effects they must show how their design and respective data meets the DiD parallel trends assumption. The parallel trends assumption that underpins the DiD methodology is not just a requirement to establish causal inference. Estimates will be biased to the degree that the DiD parallel trends assumption is not met. If the researchers feel strongly that the DiD parallel trends assumption can appropriately relaxed, and study results still achieve unbiased estimates,historical studies should be provided with DiD references included to support the claim.

RESPONSE TO REVIEWER 1:

Thank you for your comment. In the absence of several data points to test the parallel trends assumption of the DID method and to address the reviewer's comment, we have modified our approach to determine the incremental costs associated with becoming an HCU. We suggest applying the method of recycled predictions. It has been used for the purpose of estimating incremental values of various outcomes and is suitable to use in our case.

The previous description of the DID approach was deleted and replaced with the following (section "Research question 1", p.10):
"An estimate of incremental values will be generated using the method of recycled predictions. First, coefficients are obtained from a model regressing the post-values of an outcome on the HCU status, pre-values of the outcome and other covariates as needed. Then, using the calculated coefficients, predicted outcome values are estimated assuming everyone is an HCU and re-estimated assuming every subject is a non-HCU. The difference between the two averaged predictions yields the incremental value. Confidence intervals (CIs) of the incremental values will be obtained with the percentile method (i.e., creating a bootstrap distribution and assigning the 95% lower bound CI to the 2.5th percentile and the 95% upper bound CI to the 97.5th percentile). The method will be applied to analyze incremental changes in each type of costs and healthcare utilization.

This approach will allow us to account for correlation between the pre- and post values, to adjust for residual confounding by including demographic (i.e., income) and health status (i.e. comorbidities) variables in the model; and, when needed, to properly manage excessive zero values by developing two-part models. Alternative models may also be explored to accommodate the data specifics (e.g. mixed models with random effects). "

We added in the text that we may use alternative methods to accommodate the data. In particular, since we will have multiple data points for hospitalization data, including the date of admission, as described further in the manuscript, we may have an opportunity to compare the incremental values estimated by the method of recycled predictions with the DID approach.

A recent Canadian article using ICES data provides an example of the use of the DID method in the context of hospital admissions with similar data (e.g. using 1-year pre- and post index hospitalization) (Mondor L, Walker K, Bai YQ, Wodchis WP. Use of hospital-related health care among Health Links enrollees in the Central Ontario health region: a propensity-matched difference-in-differences study. CMAJ Open. 2017 Oct 12;5(4):E753-E759. doi: 10.9778/cmajo.20170054.).

Similar to this study, we will be able to verify the assumption of parallel trend during the pre-index period when comparing hospitalization between the two groups. If the assumption holds, we will compare the DID and recycled prediction methods when determining the incremental hospitalization costs associated with becoming an HCU.

Corresponding changes were made to the Method of Analysis, Appendix 3.
1. For Incremental costs (total and by care category, province wide), it reads as follows:
“Method of recycled predictions using generalized linear regression models with gamma distribution and the log link (incl. two-part models if needed)”

2. For Incremental rates of healthcare use (e.g. all cause hospital admission, physician visits and home care visits, province wide), the new text reads as follows:
“Method of recycled predictions using generalized linear regression model with negative binomial distribution and the log link (incl. two-part models if needed)"

Reviewer: 2
Reviewer Name: Prof. Dr. Van den Bussche Hendrik Institution and Country: Department of Primary Medical Care, University Medical Center Hamburg-Eppendorf, Germany Please state any competing interests: none declared

Comment 1. For a protocol of a research project, the manuscript in rather short, especially with regard to the chapters on a) Methods and Analysis and b) Analysis Plan (altogether 4,5 pages). The paper gives the impression of an application for funding developed a little further with minor changes to appear as a study protocol. Using the STROBE statement and the UCLH/UCL/RFH Biomedical Research Unit Guidelines as criteria for evaluation, one may conclude that the statistical methods are described in detail (see 2), but this is not the case for the handling of the variables, the data sets and the strategies for preventing bias. The variables of interest are only listed in the text, the datasets in a one-page appendix 1 and a (rather incomplete) list of “potential covariates” in appendix 3. It does by no way become clear which variables will be extracted from which databases and eventually grouped and/or transformed, or to which extent the 15 datasets will be matched (or not). For example, comorbidity will be captured as a patient characteristic but is remain unclear how this will be done on the basis of the “diagnostic information” available in at least 10 of the 15 datasets. On the other hand, it is not clear if morbidity will be restricted to the six special “ICES-derived cohorts” or not. Also, the manuscript does not contain any systematic description on the handling of confounders and effect modifiers. Although I recognize that it is quite complex – and pages consuming – exercise to define the handling of the datasets, the variables and the confounders, the actual version of the protocol deserves further elaboration in this respect.

RESPONSE TO REVIEWER 2, QUESTION 1:
Thank you for your feedback. We have made changes to address your comments.

To add clarity and to align the protocol better with the STROBE recommendations, key variables of interest were summarized in a table and added to what is now the new Appendix 2. The Appendix 2 shows a data source for each variable along with a brief description and the period of data availability.

As stated in the Methods, the main strategy to control for bias is matching on 3 variables at a ratio 1 HCU to 3 nonHCUs. In addition, for research questions (RQ) 1 and 3, key outcomes of interest are adjusted for certain confounders to remove their influence in a systematic way. Because the set of covariates to be used in regression models differs between the RQs, we provide a brief description of our approach within each corresponding subsection as follows:
1. Analysis plan, pp.110.
"In addition to standardized differences to compare the baseline characteristics of the two cohorts, regression methods will be used to adjust for important residual differences between the cohorts that remain after matching. Each subsection below presents more detail on handling confounding. Data preparation before running regression analyses will include identifying co-linearity between covariates."

2. Research Question 1, p.10
"This approach will allow us to account for correlation between the pre- and post values, to adjust for residual confounding by including demographic (i.e., income) and health status (i.e. comorbidities) variables in the model;"

3. Research Question 3, p.12
"The crude values will then be adjusted to remove the influence of comorbidity, demographic and care factors or RIO status."

Key potential predictors are summarized in Appendix 3. Since we do not know in advance what predictors will be included in the final prediction model that we intend to build for RQ2, we are limited in providing more specific description at this stage. Rather, we refer the reader to the Appendices. Of note, even though the STROBE checklist (or any other checklist for that matter) is often used to evaluate study protocols, it was developed for reporting study results not research intentions, hence the limitations in what is feasible to report in a protocol.

Further, as indicated in the text under "Variables", page 8, health status will be primarily captured using Expanded Diagnosis Clusters (EDCs) derived from the Johns Hopkins Adjusted Clinical Groups (ACGs). The manuscript describes the origins of this widely used classification system, while the table in the updated Appendix 2 adds detail on data sources. References are provided for an interested reader to obtain more information on the subject. Further technical detail is beyond the scope of this paper.

We also added (section on exploratory analysis, page 13) the following text to indicate that the ICES-derived cohorts are intended to facilitate exploratory subgroup analysis.

"Explanatory analyses may be conducted to explore study specific populations, cost thresholds to determine HCU status (1% vs. 5%), or any other relevant factors. ICES-derived cohorts will be used to facilitate the analysis. These cohorts were created by identifying patients with specific diseases (e.g., COPD, CHF, diabetes) using validated case-finding algorithms."

Finally, to answer the first point, we believe we were successful in describing the main methodological and analytical approaches succinctly and with enough detail for the reader to understand the proposed.

Comment 2. As stated above, the description of the approaches to answer the three main research questions contains detailed information on the statistical and econometric methods. An econometrics expert should be found to review this aspect of the paper as econometry goes beyond the qualification of the reviewer.

RESPONSE TO REVIEWER 2, QUESTION 2:

Reviewer 1 has provided a review of the statistical methods and has challenged our DID method. As a consequence, the text of the manuscript has been changed to reflect the use of recycled predictions method to determine the incremental costs associated with becoming an HCU (see response to Reviewer 1 and edits in the text).

Comment 3. The title of the paper deserves correction: a) the study is neither retrospective (nor prospective) but (one year) observational; b) the study is not a cohort-study but a casecontrol-study.

RESPONSE TO REVIEWER 2, QUESTION 3:
We respectfully disagree with the reviewer for the following reasons. Most dependent variables of interest (e.g., health costs and utilization) in the study have 2 years of data: 1 year before the HCU status and 1 year of follow up. Key baseline characteristics are derived for the year before the HCU status is reached while mortality is collected at the end of the 1 follow up period. Also, in the case of EDCs and ADGs that we use to measure the degree of (co)morbidity, we have looked back for 3 years to obtain the data.

The definition of a case-control study implies that researchers start with identifying the cases followed by controls. For this study, we retrospectively identify the cohort of elderly patients first. We then split the cohort into two groups based on exposure, i.e., HCU status, and conduct matching. We follow up for one year to collect outcome data (e.g., mortality, utilization and costs). Hence, it is a retrospective matched cohort study. We trust that this further justifies the title of the paper.

Comment 4. Independently of some critiques on the design of the study described above, I do not understand the rationale and I question the value of the study: In short: those 5% highest cost producing senior healthcare users incident in 2013 will be compared in a case control design with less cost producing users in a relation 1:3 (p. 8). Because of the incidence criterion the cases sample will consist mainly of elderly persons suffering from a very limited number of conditions (e.g. incident carcinomas with high cost therapies, sudden accidents and injuries requiring longer periods of hospitalization and/or rehabilitation and acute complications of chronic diseases (e.g. cerebral accidents on the basis of atherosclerosis). As matching will be done of the basis of age, sex and residence only, every individual in this very selective cases sample will be compared with only three controls (out of a population of several millions) who might belong – by definition – to a cost segment varying between 1% and 94% of all cost producing individuals. Therefore, the results will be difficult to generalize. This problem grows with the short observational period allowing conclusions for the first year only but none related to the more important question of persistence of HCU. Therefore, The question “whether HCU status is maintained versus an individual transitioning back to non-HCU” (p. 5) cannot be answered because of the short observation period.

RESPONSE TO REVIEWER 2, QUESTION 4:

Thank you for these comments. We agree with the last comment as we do not intend to study persistent (or prevalent) cases of HCUs. In this respect, we agree that the wording of the sentence on p.5 was confusing and part of it is now deleted. Specifically, “and whether HCU status is maintained versus an individual transitioning back to non-HCU.”

HCUs are a diverse group. Improving existing programs or identifying new opportunities are more likely when we closer study its sub-populations. In this regard, the flow of the manuscript was modified to highlight the importance of examining incident HCU cases among seniors - the second paragraph on p.2 reads as follows:

“A number of demographic and clinical characteristics of the senior HCUs have been described internationally and in Canada: high level of comorbidities, functional impairment, and poor social supports at home. However, many individual and health system characteristics related to senior HCUs are still poorly understood, especially in the context of HCU subpopulations. As such, many disease management programs as well as research efforts focus on persistent HCUs, i.e., those that retain their HCU status in subsequent years. This practice ignores the fact that “new”, or incident, HCUs have historically accounted for more than 50% of all the cases annually, including those among senior patients. Incident senior HCUs may have different characteristics than prevalent HCUs, and more focus on incident HCUs will allow for scrutiny of the factors that influence the transition from non-HCU to HCU.”

The last sentence of the paragraph highlights a major strength of the study - the” Strengths” section was modified to accordingly (below).

"• Focusing on incident senior HCUs and comparing with non-HCUs in a longitudinal study allows for scrutiny of the factors that are associated with the transition from non-HCU to HCU and for identification of opportunities of preventive management approaches
• The comparative nature of the study with a matched cohort design reduces bias due to confounding"

For more detail on the significance of the study and potential policy implications please see "RESPONSE TO REVIEWER 2 QUESTION 7"

Further, at the beginning of the study we do not know with certainty what conditions are common and cause the most suffering in the patients, what conditions are costliest, and whether the number of conditions that lead to the HCU status is very limited. The examples provided by the reviewer are all plausible possibilities that require verification for the purpose of health policy making. At the same time, previous studies suggest that the list is not as limited and includes other diagnoses (Wodchis WP, Austin PC, Henry DA. A 3-year study of high-cost users of health care. Cmaj. 2016;188(3):182-188; Clough JD, Riley GF, Cohen M, et al. Patterns of care for clinically distinct segments of high cost Medicare beneficiaries. Healthcare (Amsterdam, Netherlands). 2016;4(3):160-165).

We believe that the results will be generalizable across the province, across the country and likely applicable to other countries with a similar healthcare system for the following reasons. We plan to have access to data for all the senior HCUs in Ontario. Overall, the senior population of Ontario is approximately 2 million as of 2016 (Statistics Canada. Data products, 2016 Census. Available at http://www12.statcan.gc.ca/census-recensement/index-eng.cfm). Previous estimates of senior HCUs in the province report the number of 115,000 people in the year of 2009/2010 using the same 5% total cost threshold as in our study (Rais S, Nazerian A, Ardal S, et al. High-cost users of Ontario's healthcare services. Healthcare policy = Politiques de sante 2013;9(1):44-51). Matched to 3 controls, this yields a total sample of half a million patients, i.e., nearly 25% of the total senior population.

It should be noted that the 1 to 3 matching ratio was selected for its statistical efficiency; beyond 3 or 4 controls, the improvement in statistical power is trivial. (Mandrekar JN, Mandrekar SJ. An Introduction to Matching and its Application using SAS. SUGI 29 Proceedings, Paper 208-29, 2004; Breslow N, Day N. The Analysis of Case-Control Studies. In: Statistical Methods in Cancer Research. Lyon, France: : International Agency for Research on Cancer 1980. 169). No other changes were made to the paper in this regard.

Comment 5. The three main research question, as described in p. 7, are purely descriptive and associative but not led by hypotheses based on previous research. The number of important research questions as described in the introduction chapter is also higher than the three described, e. g. the question whether ACSC-condition do contribute to the hospital costs, the relationship between treatment costs and mortality, or the influence of physician payment models. A restriction of the number of questions might improve the quality, unless the duration and the budget of the project are unlimited (a note on the proposed duration is lacking!)

RESPONSE TO REVIEWER 2, QUESTION 5:
Many thanks for this comment. We have added a set of hypotheses to the Research Questions (p.8). This section now reads as follows:
1. What is the one-year incremental healthcare utilization and direct financial impact on public payers of becoming an incident HCU among seniors in Ontario? Hypothesis: the greatest incremental value in utilization and expenditures will be attributable to hospitalization episodes followed by physician costs.
2. What are the characteristics of hospital admissions and associated costs in senior incident HCUs compared to non-HCUs in Ontario? Hypotheses: a) causes of hospitalization as well as individual and care factors associated with an index hospitalization for senior HCUs differ from those of non-HCUs; b) the contribution of ACSCs will be high (proportion >10% of the total hospitalization costs) in senior HCUs and significantly higher than among non-HCUs
3. What is the extent of regional (health planning level) variation in healthcare utilization, costs, and mortality among senior incident HCUs compared to non-HCUs in Ontario? Hypothesis: regional variation in utilization, sector-specific costs and mortality measured by CV will be significantly higher in the HCU cohort than non-HCUs.

The research questions include a comparative analytical component in that they look at HCUs in contrast with nonHCUs. The study also uses a combination of descriptive and analytical tools to answer the research questions, including advanced statistical approaches. With respect to the information on physician payment models, these data serve two purposes- 1) to provide a better baseline description of the cohorts; 2) to be added as a covariate to a regression model exploring factors associated with index hospitalizations which is described on p.6.

To address the reviewer's comment, we have revised the manuscript to remove references to what may appear as potential research questions, e.g., the link between mortality and spending, as shown below:

4. Introduction, p. 7
DELETED: "Moreover, it is important to understand the association between variation in healthcare spending and service use with outcomes such as mortality33, which can help identify areas of potential inefficiency."

5. Research Question 3, p. 12
DELETED: “We will also assess the relationship between overall mortality and healthcare spending/utilization across the different LHINs by means of multilevel logistic regression models”

Comment 6. A study protocol should also state clearly which institution is responsible for which work package. 11 units are listed on p. 1 but any detail on responsibilities and division of labor is lacking.

RESPONSE TO REVIEWER 2 QUESTION 6: This protocol represents the outline of the PhD thesis of the lead author (SM) who takes the responsibility of the project implementation. To address this comment, we revised the “Authors Contributions”, page 13, as shown below:
“The responsibility of study implementation lies with the principle investigator (SM) that is supported and primarily supervised by JET”.

Comment 7. The justifications of the study (p. 5, para 1 and 2; p 12: “Significance an policy implications”) are vague and not very convincing. The authors themselves chose very unprecise terms, e.g. “to guide policies in Ontario”, “help identifiy (..) interventions to possibly delay hospitalizations”, or “prevent some of these patients from becoming new (persistent) HCU” etc.

RESPONSE TO REVIEWER 2 QUESTION 7: As mentioned in the Introduction section, the issue of HCUs currently affects many developed countries. More evidence is needed to guide clinicians and health administrators in policy making and program development. This section has been revised to make it more specific, and currently read as follows (p.13):

“This study will generate new knowledge that will assist Canadian healthcare administrators, clinicians, citizens and patients to guide health policy and program development around senior HCUs. The analysis of incremental healthcare utilization and costs will provide a description of the true utilization and economic impact associated with the incident HCU status. By separating index hospitalizations, the analysis of hospitalization patterns in the incident cohort of senior HCUs compared to matched non-HCUs will help identify potential interventions to prevent or divert hospitalization episodes for high risk groups. Exploring the contribution of disease-specific hospitalization costs toward the total inpatient spending will help determine the potential value expanding care models that target ACSCs and identify opportunities of fund re-allocation to hospitalizations types that are more contributory and more amenable to change. Further, by defining regional variation in healthcare services and spending among senior HCUs we will inform the value of potential benchmarking and regional practice comparisons in HCU management. Finally, since other jurisdictions in developed countries have comparable health systems and are faced with similar HCU challenges, our methods and findings may inform local considerations for HCU prevention and management.”

Reviewer: 3
Reviewer Name: Robert C Amland
Institution and Country: Cerner Corporation, USA Please state any competing interests: None declared

Comment: Thank you for submitting this research prospectus. A major concern is measurement error on sepsis diagnosis codes. Sepsis is lethal, about 1 in 2 in-hospital deaths associated with sepsis in USA, and likely the most expensive condition for in-hospital care. Sepsis has been shown to be under-documented in electronic health record systems, which reduces diagnosis code assignment at discharge. How will this proposed study address this serious limitation with measurement error? Please refer to the following recent study, which reports sensitivity of sepsis using diagnosis code methodology is approximately 30%, which suggests 70% sepsis patients have a different diagnosis code at discharge. Several quality improvement studies in USA have corroborated this concern. Thank you for considering this substantial problem which impacts the statistical analysis methodology. Please refer to recent article: Rhee C, Dantes R, Epstein L, et al. Incidence and trends in US hospitals using clinical vs claims data, 2009-2014. JAMA. Published online September 13, 2017. Thank you again.

RESPONSE TO REVIEWER 3:
Thank you for commenting and bringing this important issue to our attention. Indeed, there are various approaches to flag a condition within administrative databases: claims -based (currently most widely used) and EMR-based (emerging, reportedly more accurate). The discrepancy that may exist between these two, plus with what is clinically observed is a well recognized limitation of using administrative databases for research purposes. However, as noted by Rhee C. et al., the use of administrative data has been increasing while coding practices and approaches are improving. Our dataset was derived from a data repository hosted by the Institute for Clinical Evaluative Sciences (ICES) which has an international reputation of a trusted source of high-quality healthcare evidence.

As the sophisticated EMR-based case identification algorithm described by the paper relies on multiple clinical criteria instead of diagnosis codes, it is more challenging to implement. For that reason, many researchers resort to claims-based estimates with comparable end results. For sepsis specifically, although Rhee C. et al. reveal a lower sensitivity of claims-based estimates of sepsis incidence compared to the EMR, the positive predicted values (PPV) are relatively high and comparable (75.2% vs 70.4%, respectively, p=0.23).

To further improve the sensitivity of our MRDX-based algorithm to capture sepsis cases, we will update it to look for sepsis cases among “pre-admission” and “post-admission” diagnosis codes: this will allow us to identify sepsis cases whenever they were diagnosed during a hospitalization episode but were not labeled as MRDX upon discharge. This will be part of sensitivity analysis.
As a result, we have revised a paragraph on sensitivity analysis under Research question 2, p.12. to address this important comment and added the reference as suggested by the reviewer. It now reads as follows:

“Sensitivity analysis will be conducted to assess the impact of several factors on hospitalization costs. Analysis will be repeated for 3 age subgroups: those age 66 to 74, 75 to 84, and 85 and older. As sepsis cases (reportedly, one of the costliest among hospitalized conditions) may go underreported when using MRDX codes alone58, the case-finding algorithm to capture these cases will include preadmission and postadmission codes that are not MRDX. We will also apply the ACSC algorithm excluding non-emergent hospitalizations and re-admissions. The ACSC related costs will be compared to non-ACSC inpatient costs in both cohorts”.

VERSION 2 – REVIEW

REVIEWER	Robert C Amland Cerner Corporation, USA
REVIEW RETURNED	17-Nov-2017

GENERAL COMMENTS	Thank you for this revised manuscript; well done.