PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of consumer co-payments for subsidised medicines on health services use and outcomes: a protocol using linked administrative data from Western Australia
AUTHORS	Seaman, Karla; Sanfilippo, Frank; Roughead, Elizabeth; Bulsara, Max; Kemp, Anna; Bulsara, Caroline; Watts, Gerald; Preen, David

VERSION 1 - REVIEW

REVIEWER	Vera Lucia Luiza Sergio Arouca National School of Public Health - Brazil
REVIEW RETURNED	19-Sep-2016

GENERAL COMMENTS	The objective is not clearly stated, neither in the Abstract or in the Background sections. Text is kind of confusing. Periods of time to be studied are not clearly presented. Table 2 is good, but it is not reflected in the text. It is not explained how confounders will be controlled.

REVIEWER	Joanna Kopinska CEIS, University of Rome Tor Vergata
REVIEW RETURNED	14-Nov-2016

GENERAL COMMENTS	The study protocol of Seaman et al. reports the study design based on linked administrative data, which potentially represents a very interesting and thorough analysis of the impact of co-payments with a large sample size and objective data. It also takes advantage of objective individual level data to evaluate the indirect impact of co-payments on outcomes such as GP visits, hospitalizations and mortality. The protocol is clear and detailed with sufficient scientific credibility to make me think that the work deserves publication upon few minor issues regarding the methods employed to analyze the data. My suggestion is that with a dataset containing dispensing records for 260,000 thousand patients, where such a large sample size is important in its own right, it would be interesting to see other analytical tools applied in order to explore the richness of the data. The introduction of the 21% increase in the co-payments imposes a sort of natural experiment for the statin-users, where an exogenous variation of the underlying drug availability might have introduced an exogenous shift in the adherence patterns, very difficult to observe in other conditions. A difference-in-differences approach to the data analysis might be appropriate in this case, where the authors could study the differential effect of the co-payments introduction on a treatment group (statin takers undergoing co-payments increase) vs.

	the control group (statin users whose statin types are below the general copayment). One could thus exploit the time driven average change of the control vs. treatment group outcomes to establish the causal link between co-payments and adherence. Perhaps, also the Instrumental Variables approach could be applied to the analysis of the impact of copayments on hospitalization, mortality, concomitant therapies and other outcomes. Again, one could use the exogenous variation in the co-payment scheme in order to instrument for the adherence to statins. In such a way, only the exogenous part of the variation in adherence could be isolated, and the subsequent link between individual adherence and other health outcomes could be strengthened by causality claims, net of the endogeneity which might impact both adherence and health outcomes due to other factors or reverse causality issues.

REVIEWER	Emily Walkom Research Academic, The University of Newcastle, Australia.
REVIEW RETURNED	11-Jan-2017

GENERAL COMMENTS	Thank you for the opportunity to review this protocol. The results are sure to be interesting and informative. I have a couple of minor comments. Page 7 line 21 - it might be beneficial to some readers to briefly explain what the stockpiling phenomenon means and why it occurs. Whilst the information on ethics approval was clear, it would be helpful to add within the text some details on patient consent - or clarify that the process involved in examining data from the linked databases was such that patient consent was not required. A couple of minor typos: Abstract Page 2 line 24 "a cohort" Page 7 line 53 "arguably" Page 8 line 1 type "of" statin user. Page 9 line 19 "education".

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
The objective is not clearly stated, either in the Abstract or in the Background sections.
The following information has been added to the abstract and the objectives of our study are stated on page 4 of the revised manuscript.
“The aim of this study is to determine the demographic and clinical characteristics of individuals ceasing or reducing statin medication use following the January 2005 PBS co-payment increase, and the effects on their health outcomes.”

Text is kind of confusing.
It is difficult to respond to this comment given the lack of specific examples or instances in the text which the reviewer found “confusing”. In addition, we note that this issue was not raised by either of the other two reviewers and indeed Reviewer 2 wrote “The protocol is clear…”. However, to attempt to address any such issues, a review of the text has been conducted by all authors to improve clarity.
Periods of time to be studied are not clearly presented.

To clarify the observation period for this study we have added the following text to page 6:
"The study period will vary for each objective ranging from 1 January 2000 to 31 December 2010."
In addition, we have also added further details regarding study time periods throughout the text, for two of the objectives on page 4 and under each objective in the statistical analysis section on page 8.
Table 2 is good, but it is not reflected in the text.
Specific reference to Table 2 has been added to the relevant section of the manuscript text.
It is not explained how confounders will be controlled.
As noted in the statistical analysis section of the manuscript, confounders will be controlled by utilising different modelling techniques such as multivariate logistic regression, multivariate Cox proportional hazards regression and generalized estimating equation (GEE) modelling, depending on the outcome under focus. The following has been added to the statistical section, "Additionally, stratification by beneficiary status will be conducted."
Reviewer 2:
The study protocol of Seaman et al. reports the study design based on linked administrative data, which potentially represents a very interesting and thorough analysis of the impact of co-payments with a large sample size and objective data. It also takes advantage of objective individual level data to evaluate the indirect impact of co-payments on outcomes such as GP visits, hospitalizations and mortality. The protocol is clear and detailed with sufficient scientific credibility to make me think that the work deserves publication upon few minor issues regarding the methods employed to analyze the data.

My suggestion is that with a dataset containing dispensing records for 260,000 thousand patients, where such a large sample size is important in its own right, it would be interesting to see other analytical tools applied in order to explore the richness of the data. The introduction of the 21% increase in the co-payments imposes a sort of natural experiment for the statin-users, where an exogenous variation of the underlying drug availability might have introduced an exogenous shift in the adherence patterns, very difficult to observe in other conditions. A difference-in-differences approach to the data analysis might be appropriate in this case, where the authors could study the differential effect of the co-payments introduction on a treatment group (statin takers undergoing co-payments increase) vs. the control group (statin users whose statin types are below the general copayment). One could thus exploit the time driven average change of the control vs. treatment group outcomes to establish the causal link between co-payments and adherence.

Perhaps, also the Instrumental Variables approach could be applied to the analysis of the impact of co-payments on hospitalization, mortality, concomitant therapies and other outcomes. Again, one could use the exogenous variation in the co-payment scheme in order to instrument for the adherence to statins. In such a way, only the exogenous part of the variation in adherence could be isolated, and the subsequent link between individual adherence and other health outcomes could be strengthened by causality claims, net of the endogeneity which might impact both adherence and health outcomes due to other factors or reverse causality issues.
We agree that a difference-in-difference analysis would add value to the study, however, due to the limitations of the data we are unable to create an appropriate control group, restraining our ability to conduct this analysis. The limitation is due to the time period we are exploring, as any medication dispensed under the PBS co-payment is not captured in the dataset before 2012. Consequently, we have PBS data from 2002 to 2010 hence we are unable to create a control group.
The Instrumental Variable approach suggested by the Reviewer is an interesting idea and would represent a powerful approach if an appropriate instrument could be identified. However, the criteria for a valid instrument is that the variable needs to be strongly associated with the exposure but have no relationship with the outcome. Our study cohort was sampled based on patients taking statin medication in 2004. As such, the use of time as an instrumental variable (ie, pre-2005 vs 2005 onwards) would not be appropriate because there is a greater likelihood of adverse cardiovascular event over time for this population, especially given they were all known to have cardiovascular

disease upon study entry.
Reviewer 3:
Thank you for the opportunity to review this protocol. The results are sure to be interesting and informative.

I have a couple of minor comments.

Page 7 line 21 - it might be beneficial to some readers to briefly explain what the stockpiling phenomenon means and why it occurs.
The following definition has been added to the revision on page 7.
“This phenomenon occurs when consumers reach the safety net spending threshold for PBS medicines and are entitled to free medicines or a reduced co-payment for the remainder of the calendar year. This can result in consumers filling additional prescriptions toward the end of the year before they return to their usual co-payment the following January.”

Whilst the information on ethics approval was clear, it would be helpful to add within the text some details on patient consent - or clarify that the process involved in examining data from the linked databases was such that patient consent was not required.
The following definition has been added to the revision on page 9.
“A wavier of consent was approved by the HREC bodies to provided linked de-identified databases to the researchers to conduct this study.”

A couple of minor typos:
Abstract Page 2 line 24 "a cohort". Corrected
Page 7 line 53 "arguably" . Corrected
Page 8 line 1 type "of" statin user. Corrected
Page 9 line 19 "education". Corrected

VERSION 2 – REVIEW

REVIEWER	JOANNA KOPINSKA CEIS, UNIVERSITY OF ROME TOR VERGATA, ITALY
REVIEW RETURNED	21-Mar-2017

GENERAL COMMENTS	The revised study protocol of Seaman et al. will sure deliver an interesting and thorough analysis based on a large sample of individual level objective data, evaluating the indirect impact of co-payments on outcomes such as GP visits, hospitalizations and mortality. The protocol is clear and detailed with sufficient scientific credibility to make me think that the work deserves publication. I accept the discussion provided by the corresponding author and the minor revisions made.