PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A National Surveillance Project on Chronic Kidney Disease Management in Canadian Primary Care: A Study Protocol
AUTHORS	Bello, A; Ronksley, Paul; Tangri, Navdeep; Singer, Alexander; Grill, Allan; Nitsch, Dorothea; Queenan, John; Lindeman, Cliff; Soos, Boglarka; Freiheit, Elizabeth; Tuot, Delphine; Mangin, Dee; Drummond, Neil

VERSION 1 - REVIEW

REVIEWER	Dr Nicola Thomas London South Bank University, UK
REVIEW RETURNED	23-Feb-2017

GENERAL COMMENTS	The authors are presenting a protocol for a retrospective observational study on the epidemiology and management of CKD in primary care. The authors recognise that few countries have effective surveillance mechanisms for chronic kidney disease and are proposing a nationwide system in Canada. The objectives of the study are well-defined, although objective 3 which focuses on 'processes of care for CKD' could be explained more clearly and in more detail. It could be argued that process-based outcomes for CKD do not solely include clinical measures such as eGFR, BP, ACR etc, but rather include other important measures such as self-management support or patient-reported experience measures. Discussion on why 'quality measures' such as these are not included in the protocol should be included. The secondary analysis of patients with eGFR <45 was justified clearly and this has important clinical implications. Although it is commended that relevant stakeholders (patients, practitioners, policymakers) have been involved from inception, more detail on this would be interesting for the reader. For example, how exactly were patients involved: where did they come from; how exactly did they shape the proposal etc. Overall though an interesting protocol with very important benefits for patients and healthcare systems alike.

REVIEWER	Tom Blakeman The University of Manchester, United Kingdom I am a member of the national Think Kidneys Programme Board in England and I am Clinical-Academic Lead for the NIHR CLAHRC Greater Manchester Kidney Health Programme

REVIEW RETURNED	25-Mar-2017

GENERAL COMMENTS	Thank you for inviting me to review this manuscript and planned programme of work, which I think has the potential to improve health outcomes. I think the paper would benefit from a more thorough critique of the strengths and limitations of the approach being taken. In doing so, this would enhance the its potential to be a key exemplar for the design and implementation of data bases to improve the delivery of care for people with chronic kidney disease. Thank you for inviting me to review this manuscript. My critique is taken from a perspective of having an interest in the management of chronic kidney disease in primary care. I do not have experience of establishing a large data base or of conducting 'retrospective observational studies.' The planned work is of major importance and has the potential to improve health care delivery and outcomes. The following comments are written with a view to enhance the paper and the proposed objectives. Overall, I think the paper would benefit from a more detailed critique about the strengths and weaknesses of the planned development and use of the CKD database. In terms of writing style, the paper may benefit from tightening with greater clarity of the issues raised. Specific points include: Page 3 Line 21 The authors state: 'The study leverages retrospective data collected at point of care, and therefore limitations include variable data quality and incomplete information in some patient domains' I think it would be helpful if more detail was provided in the main text concerning the methodological limitations of the proposed approach. Page 4 Line 27: It might be helpful for the reader to be more explicit about which countries have developed CKD Surveillance systems. With that, have the authors compared their approach to development of a surveillance system in Canada. E.g. is there a common approach validate a case definition of CKD? Methods *Setting:* It might helpful to provide the reader with more detail about the healthcare systems in the 10 provinces and the 3 territories. (e.g. are they capitation based system or fee for services systems? Are there differences? Have these changed over the time frames outlined? (i.e. 2010 to 2015, and from 2016 onwards). Being explicit about the differing contexts may help understand future interpretation of the data and any variation across regions *Identification of CKD:* The authors state that individuals will be defined as having CKD using the CKD-EPI Equation. It would be helpful to know when the CKD-EPI equation was introduced in each province and territory. See also: http://bmjopen.bmj.com/content/bmjopen/1/2/e000308.full.pdf

	On page 6 line 8, the authors state 'We recognize the significant limitations of the ICD-9 codes when applied for CKD identification in the community, however, its use will allow us to capture those patients with CKD who may or may not have had an abnormal eGFR.' It would be helpful if the authors were more explicit about these 'significant limitations' either in the methods section or in the discussion. E.g. If used, how will future analysis determine evidence of CKD progression. Is the approach being taken to define CKD consistent with other surveillance systems internationally? It would be helpful for the authors to clarify whether it is possible to differentiate renal function tests taken in a stable clinical state versus those taken during an episode of acute illness, in which an acute change may reflect Acute Kidney Injury rather than underlying CKD. Will this be included in the validation process entailing 'random sampling of 1000 CPCSSN charts.' It would be helpful if the authors could provide more detail about this validation exercise. The authors indicate that the surveillance system is being developed in terms of CKD in the context of vascular health. There is no mention of Acute Kidney Injury in the text or tables. Recognising that a relationship exists between CKD and AKI (i.e. CKD a risk factor for AKI during episodes of acute illness and AKI a predictor of CKD progression), the authors may wish to consider its inclusion in future developments. *Evaluation of processes of care:* Suggest more detail is provided here. Currently limited and slightly vague (e.g. 'This entails monitoring for the classical risk parameters…' **Ethics and Dissemination** It may be helpful to split and amend this subheading. In order to support the dissemination of good practice, it would be helpful for the authors to provide the reader with greater understanding of the key ethical and governance issues underpinning the establishment and implementation of the surveillance network. The 'dissemination' section is rather general and limited in detail. E.g. I'm unsure of the benefit to the reader of stating 'The results will be published in leading general medicine, nephrology and primary care peer-reviewed journals and presented at relevant national and international scientific meetings.' I suggest more specific detail for this section, which may help the reader have greater clarity on the purpose in the development of the database and surveillance system. It may be helpful to provide greater clarity on how the development of the CKD surveillance system relates to improvement/implementation science methodologies. It would be helpful to understand how the evidence base around Improvement Science has or has not informed the design of the system. It would also be helpful to understand how the surveillance system has been designed to support future research. Are there any guidelines to support the development of databases to support

	'retrospective observational studies'? If not, is there an opportunity for this work to be an exemplar of how to optimise the development of a national surveillance network. The authors may find it helpful to refer to the reports by the ISPOR Task Force on Retrospective Databases: http://www.equator-network.org/reporting-guidelines/good-research-practices-for-comparative-effectiveness-research-defining-reporting-and-interpreting-nonrandomized-studies-of-treatment-effects-using-secondary-data-sources-the-ispor-good-research-pr/ See also: https://www.ncbi.nlm.nih.gov/pubmed/12641858 The paper focuses on the improving process measures of care. It would be helpful to make explicit if there are any future plans to use the surveillance system to evaluate health outcomes. E.g. linkage to other databases etc. progression of CKD, CVD outcomes, ESRD, episodes of illness complicated by AKI. If so, how will this be achieved?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
The authors are presenting a protocol for a retrospective observational study on the epidemiology and management of CKD in primary care. The authors recognise that few countries have effective surveillance mechanisms for chronic kidney disease and are proposing a nationwide system in Canada.

The objectives of the study are well-defined, although objective 3 which focuses on 'processes of care for CKD' could be explained more clearly and in more detail.
Response: This has been done. (page 6-7, lines 234-254).

It could be argued that process-based outcomes for CKD do not solely include clinical measures such as eGFR, BP, ACR etc, but rather include other important measures such as self-management support or patient-reported experience measures. Discussion on why 'quality measures' such as these are not included in the protocol should be included.

Response: This has been done. This is discussed as a limitation with this database (page 9, lines 347-354).

The secondary analysis of patients with eGFR <45 was justified clearly and this has important clinical implications.
Response: Thank you.

Although it is commended that relevant stakeholders (patients, practitioners, policymakers) have been involved from inception, more detail on this would be interesting for the reader. For example, how exactly were patients involved: where did they come from; how exactly did they shape the proposal etc.
Response: This has been done (Page 9, lines 299-305).

Overall though an interesting protocol with very important benefits for patients and healthcare systems alike.
Response: Thank you.

Reviewer: 2
Thank you for inviting me to review this manuscript and planned programme of work, which I think has the potential to improve health outcomes.
Response: Thank you.

I think the paper would benefit from a more thorough critique of the strengths and limitations of the approach being taken. In doing so, this would enhance the its potential to be a key exemplar for the design and implementation of data bases to improve the delivery of care for people with chronic kidney disease. In terms of writing style, the paper may benefit from tightening with greater clarity of the issues raised. Specific points include:

Page 3 Line 21 The authors state: 'The study leverages retrospective data collected at point of care, and therefore limitations include variable data quality and incomplete information in some patient domains' I think it would be helpful if more detail was provided in the main text concerning the methodological limitations of the proposed approach.
Response: This has been done (page 9, lines 347-352).

Page 4 Line 27: It might be helpful for the reader to be more explicit about which countries have developed CKD Surveillance systems. With that, have the authors compared their approach to development of a surveillance system in Canada. E.g. is there a common approach validate a case definition of CKD?
Response: This has been done (page 4, lines 101-132), and a new Table 3 is now added comparing the major surveillance systems across countries.

Methods Setting: It might helpful to provide the reader with more detail about the healthcare systems in the 10 provinces and the 3 territories. (e.g. are they capitation based system or fee for services systems? Are there differences? Have these changed over the time frames outlined? (i.e. 2010 to 2015, and from 2016 onwards). Being explicit about the differing contexts may help understand future interpretation of the data and any variation across regions Identification of CKD.
Response: This has been done (page 5, lines 154-163).

The authors state that individuals will be defined as having CKD using the CKD-EPI Equation. It would be helpful to know when the CKD-EPI equation was introduced in each province and territory. See also: http://bmjopen.bmj.com/content/bmjopen/1/2/e000308.full.pdf 2
Response: We are not using laboratory reported eGFR in these analyses, and this is made more explicit in the relevant section of the text (page 6, lines 208-217).

On page 6 line 8, the authors state 'We recognize the significant limitations of the ICD-9 codes when applied for CKD identification in the community, however, its use will allow us to capture those patients with CKD who may or may not have had an abnormal eGFR.' It would be helpful if the authors were more explicit about these 'significant limitations' either in the methods section or in the discussion. E.g. If used, how will future analysis determine evidence of CKD progression. Is the approach being taken to define CKD consistent with other surveillance systems internationally?

Response: The use of ICD code in this analysis is restricted to the evaluation of CKD identification by primary care practitioners (determines the rate at which CKD is being coded on EMR when CKD defining criteria are met). This is now made more explicit in the relevant section of the text (page 6,

lines 214-217).
It would be helpful for the authors to clarify whether it is possible to differentiate renal function tests taken in a stable clinical state versus those taken during an episode of acute illness, in which an acute change may reflect Acute Kidney Injury rather than underlying CKD. Will this be included in the validation process entailing 'random sampling of 1000 CPCSSN charts.' It would be helpful if the authors could provide more detail about this validation exercise.
Response: In all our definitions criteria for CKD "chronicity" criteria must be met as CKD will be defined using two values of eGFR >90 days apart. This would mitigate the risk of including cases of acute kidney injury in our cohort.

The authors indicate that the surveillance system is being developed in terms of CKD in the context of vascular health. There is no mention of Acute Kidney Injury in the text or tables. Recognising that a relationship exists between CKD and AKI (i.e. CKD a risk factor for AKI during episodes of acute illness and AKI a predictor of CKD progression), the authors may wish to consider its inclusion in future developments.
Response: This study focused on CKD, and as this is routine data from community-based ambulatory care practices, it would be difficult to reliably capture patients with acute kidney injury. This may be considered for future work following a validation study.

Evaluation of processes of care: Suggest more detail is provided here. Currently limited and slightly vague (e.g. 'This entails monitoring for the classical risk parameters…'
Response: This has been done (page 7, lines 237-254).

Ethics and Dissemination It may be helpful to split and amend this subheading. In order to support the dissemination of good practice, it would be helpful for the authors to provide the reader with greater understanding of the key ethical and governance issues underpinning the establishment and implementation of the surveillance network. The 'dissemination' section is rather general and limited in detail. E.g. I'm unsure of the benefit to the reader of stating 'The results will be published in leading general medicine, nephrology and primary care peer-reviewed journals and presented at relevant national and international scientific meetings.' I suggest more specific detail for this section, which may help the reader have greater clarity on the purpose in the development of the database and surveillance system.
Response: This was based on the protocol guideline provided by the journal. We have therefore not separated this section to keep in tune with the guideline provided by the journal. The highlighted issues are addressed in the relevant section (page 8, lines 299-305)

It may be helpful to provide greater clarity on how the development of the CKD surveillance system relates to improvement/implementation science methodologies. It would be helpful to understand how the evidence base around Improvement Science has or has not informed the design of the system. It would also be helpful to understand how the surveillance system has been designed to support future research. Are there any guidelines to support the development of databases 3 to support 'retrospective observational studies'? If not, is there an opportunity for this work to be an exemplar of how to optimise the development of a national surveillance network. The authors may find it helpful to refer to the reports by the ISPOR Task Force on Retrospective Databases: http://www.equator-network.org/reporting-guidelines/good-research-practices-forcomparative-effectiveness-research-defining-reporting-and-interpreting-nonrandomizedstudies-of-treatment-effects-using-secondary-data-sources-the-ispor-good-research-pr/ See also: https://www.ncbi.nlm.nih.gov/pubmed/12641858
Response: These guidelines refer to reporting of results following retrospective cohort studies but not specific to study protocols. These references are now cited as reporting frameworks for the study results (page 9, line 340-341).

The paper focuses on the improving process measures of care. It would be helpful to make explicit if there are any future plans to use the surveillance system to evaluate health outcomes. E.g. linkage to other databases etc. progression of CKD, CVD outcomes, ESRD, episodes of illness complicated by AKI. If so, how will this be achieved?
This has been done (page 9,

VERSION 2 – REVIEW

REVIEWER	Prof Nicola Thomas London South Bank University, UK
REVIEW RETURNED	22-May-2017

GENERAL COMMENTS	Thank you for addressing all the reviewers' comments and suggestions. The paper has been strengthened and I am now able to recommend for publication.

REVIEWER	Tom Blakeman The University of Manchester, United Kingdom Member of Think Kidneys Programme Board, UK.
REVIEW RETURNED	24-May-2017

GENERAL COMMENTS	Thank you for responding to my previous queries and suggestions, which in the main are adequately addressed. To address my misunderstanding, I would be grateful for greater clarity on the following points: As stated on page 7 line 245, is a key focus to 'determine the proportion of patients with CKD and correctly coded as having CKD'? If so, then I would be grateful for greater clarity in your response: 'We are not using laboratory reported eGFR in these analyses, and this is made more explicit in the relevant section of the text (page 6, lines 208-217). Also, I suggest updating the methods section of the abstract so that it is more closely aligned with the objectives stated on page 7

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Prof Nicola Thomas
Institution and Country: London South Bank University, UK
Please state any competing interests: None declared

Please leave your comments for the authors below

Thank you for addressing all the reviewers' comments and suggestions. The paper has been strengthened and I am now able to recommend for publication.
Thank you.

Reviewer: 2
Reviewer Name: Tom Blakeman
Institution and Country: The University of Manchester, United Kingdom
Please state any competing interests: Member of Think Kidneys Programme Board, UK.

Thank you for responding to my previous queries and suggestions, which in the main are adequately addressed.
Thank you.

To address my misunderstanding, I would be grateful for greater clarity on the following points:

As stated on page 7 line 245, is a key focus to 'determine the proportion of patients with CKD and correctly coded as having CKD'?

If so, then I would be grateful for greater clarity in your response: 'We are not using laboratory reported eGFR in these analyses, and this is made more explicit in the relevant section of the text (page 6, lines 208-217).
Response: Serum creatinine (Scr) measurements will be used to calculate estimated glomerular filtration rate (eGFR) using CKD-EPI equation. Wee will be using calculated eGFR instead of the eGFR records reported by labs due to discrepancies in the reporting across labs in the country.
Pls see page 6, lines 212-214.

Also, I suggest updating the methods section of the abstract so that it is more closely aligned with the objectives stated on page 7.
Response: This has been done

VERSION 3 – REVIEW

REVIEWER	Tom Blakeman The University of Manchester Member of Think Kidneys Programme Board
REVIEW RETURNED	01-Jun-2017

GENERAL COMMENTS	The authors have amended the abstract though I suggest a minor change to the wording for it to make sense to the reader. On page 2 line 21, do the authors mean '...an enable us to: 1) determine the prevalence of CKD burden.... I am happy for the editorial team to clarify this with the authors