PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of e-Alert for Detection of Acute Kidney Injury on Processes of Care and Outcomes: Protocol for a Systematic Review and Meta-Analysis
AUTHORS	Lachance, Philippe; Villeneuve, Pierre-Marc; Wilson, Francis; Selby, Nicholas; Featherstone, Robin; Rewa, Oleksa; Bagshaw, Sean

VERSION 1 - REVIEW

REVIEWER	Zhongheng Zhang Jinhua municipal central hospital P.R.China
REVIEW RETURNED	05-Feb-2016

GENERAL COMMENTS	This is a well written protocol that defines nearly all necessary materials for conducting a systematic review. However, I have several small suggestion on this paper. 1. The e-alert system is primarily based on serum creatinine and urine output (as defined by (KDIGO, RIFLE, AKIN)), However this cannot reflect the early phase of AKI. for instance, NGAL and CyC can be much early than creatinine and urine output (Am J Kidney Dis. 2011 Sep;58(3):356-65. Heart Lung Vessel. 2015;7(1):64-73.). Also there are some evidence that lactate can also be a biomarker of early recognition of AKI (PLoS One. 2015 Mar 30;10(3):e0120466. doi: 10.1371/journal.pone.0120466. eCollection 2015.). These biomarkers may have not been incorporated into the e-alert system, but these can be discussed. 2. There is a newly published protocol for systematic review and meta-analysis called ROBIS (J Clin Epidemiol. 2016 Jan;69:225-34. doi: 10.1016/j.jclinepi.2015.06.005). Do you think this will be beneficial to enhance the quality of review? However, this may result in significant changes to the present study protocol. thus it is compulsory. 3. How do you handle evidences from observational studies and RCT? evidence from these two types of studies are different. one way is to use Bayesian approach that incorporate observational evidence as prior. Then the strength of the prior can be denoted a power (for methodology can be referenced from one of our previous publication [BMJ Open. 2015 Jan 16;5(1):e006524.]). However this method is criticized for a subjective judgment, and it may not be good. 4. meta-regression is best suit to continuous covariates. but in this study the predefined covariates are all categorical variables, why not simply use subgroup analysis to explore heterogeneity?

REVIEWER	Kianoush Kashani Mayo Clinic USA I have no conflict of interest although my research is focused on the same field.
REVIEW RETURNED	27-Feb-2016

GENERAL COMMENTS	Lachance et al. described a protocol for a systematic analysis of literature available on the impact of electronic alerts on the AKI processes of care and outcomes. Strengths: - Introduction provides an excellent rationalization for such systematic analysis - This is a well-written paper with clear language and logical flow - Such systematic analysis is needed at this time to allow the readers decide if e-alerts provide any benefit to the patients. - Inclusion of at least two languages for search - Excellent description of systematic analysis methodology Concerns: - This script summarizes the main steps of a systematic analysis which mostly is common with the systematic analysis of other fields (other than e-alert); therefore, it may not add significantly to the body of knowledge nor fill any knowledge gap.

VERSION 1 – AUTHOR RESPONSE

Response Reviewer 1 Comments:
1. The e-alert system is primarily based on serum creatinine and urine output (as defined by (KDIGO, RIFLE, AKIN)), However this cannot reflect the early phase of AKI. for instance, NGAL and CyC can be much early than creatinine and urine output (Am J Kidney Dis. 2011 Sep;58(3):356-65. Heart Lung Vessel. 2015;7(1):64-73.). Also there are some evidence that lactate can also be a biomarker of early recognition of AKI (PLoS One. 2015 Mar 30;10(3):e0120466. doi: 10.1371/journal.pone.0120466. eCollection 2015.). These biomarkers may have not been incorporated into the e-alert system, but these can be discussed.

In general, we agree with the reviewer. There are a number of limitations associated with the use of creatinine and urine output to diagnose and classify AKI. We also agree with the reviewer that novel biomarkers (i.e., NGAL) and other serum markers (i.e., lactate) may have complementary roles in the diagnosis and staging of AKI. However, the vast majority of novel biomarkers have not been routinely integrated or implemented into bedside practice and their precise role for informing about clinical decision support remain uncertain. Others mentioned are not necessarily routine or available for all patients who are at risk or have developed AKI in all settings (i.e., such as lactate). Importantly, none of the suggested biomarkers have been integrated into consensus classification schemes for AKI. For all these reasons, these have yet to be integrated or evaluated into automated e-alerts and therefore will not be a primary focus of this systematic review. We will naturally address some of these limitations of the consensus definitions, as identified in the studies selected for inclusion, in our final manuscript.

2. There is a newly published protocol for systematic review and meta-analysis called ROBIS (J Clin Epidemiol. 2016 Jan;69:225-34. doi: 10.1016/j.jclinepi.2015.06.005). Do you think this will be

beneficial to enhance the quality of review? However, this may result in significant changes to the present study protocol. thus it is compulsory.

We appreciate the reviewer's comment. We do not believe we need to integrate the ROBIS tool in our review. As stated by the authors of this article, the ROBIS tool is primarily used to assess the risk of bias of a completed systematic review and to be used by guideline developers, authors of reviews and peer reviewers. We do not believe this is applicable for our systematic review at this time. Moreover, we believe the PRISMA guidelines represent a comprehensive and transparent mechanism to report our systematic review.

3. How do you handle evidences from observational studies and RCT? evidence from these two types of studies are different. one way is to use Bayesian approach that incorporate observational evidence as prior. Then the strength of the prior can be denoted a power (for methodology can be referenced from one of our previous publication [BMJ Open. 2015 Jan 16;5(1):e006524.]). However this method is criticized for a subjective judgment, and it may not be good.

We appreciate the reviewers comment. As outlined in our protocol, we propose to perform stratified and sensitivity analyses by study design and risk of bias (see page 9, lines 220-222) to explore the quality and robustness of evidence describing the use of e-alerts in AKI.

4. Meta-regression is best suit to continuous covariates. but in this study the predefined covariates are all categorical variables, why not simply use subgroup analysis to explore heterogeneity?

Subgroup sensitivity analysis and meta-regression where possible will be performed. We modified the text in the analysis section accordingly (see page 9, line 217-219).

Response to Reviewer #2 Comments
1. This script summarizes the main steps of a systematic analysis which mostly is common with the systematic analysis of other fields (other than e-alert); therefore, it may not add significantly to the body of knowledge nor fill any knowledge gap.

We appreciate the reviewer's comment. This manuscript is intended to provide a transparent a priori detailed summary of how we propose to perform our systematic review. We recognize that our protocol document will not "add significantly to the body of knowledge"; however, we expect the completed review will certainly inform about the quality of the evidence base, summarize the evidence on the efficacy and effectiveness of e-alerts to improve processes of care, quality of care and outcomes for patients with AKI and identify key knowledge gaps to focus future research effort.

VERSION 2 – REVIEW

REVIEWER	Zhongheng Zhang Jinhua municipal central hospital China
REVIEW RETURNED	22-Mar-2016

GENERAL COMMENTS	In the previous review I presented several comments but the authors simply overlooked them with some rebuttal. The purpose of my previous suggestion is to improve the manuscript, so in this version I still insist that several modifications should be made. for example, the first comment is as follows: 1. The e-alert system is primarily based on serum creatinine and

	urine output (as defined by (KDIGO, RIFLE, AKIN)), However this cannot reflect the early phase of AKI. for instance, NGAL and CyC can be much early than creatinine and urine output (Am J Kidney Dis. 2011 Sep;58(3):356-65. Heart Lung Vessel. 2015;7(1):64-73.). Also there are some evidence that lactate can also be a biomarker of early recognition of AKI (PLoS One. 2015 Mar 30;10(3):e0120466. doi: 10.1371/journal.pone.0120466. eCollection 2015.). These biomarkers may have not been incorporated into the e-alert system, but these can be discussed. I know to utilize NGAL is difficult in routine clinical practice, but at least this point should be discussed with citations of relevant references.