Impact of e-Alert for Detection of Acute Kidney Injury on Processes of Care and Outcomes: Protocol for a Systematic Review and Meta-Analysis (Appendix)
### Appendix 1. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

| Section and topic | Item No | Checklist item |
|-------------------|---------|----------------|
| **ADMINISTRATIVE INFORMATION** | | |
| Title: | | |
| Identification | 1a | Identify the report as a protocol of a systematic review  
*See page 1, line 2* |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such  
**NOT APPLICABLE** |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number  
*See page 6, lines 136-137* |
| Authors: | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author  
*See page 1, lines 5-21* |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review  
*See page 11, line 259-261* |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments  
**NOT APPLICABLE** |
| Support: | | |
| Sources | 5a | Indicate sources of financial or other support for the review  
*See page 11, line 266* |
| Sponsor | 5b | Provide name for the review funder and/or sponsor  
*See page 11, line 266* |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol  
*See page 11, line 266* |
| **INTRODUCTION** | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known  
*See pages 3-4, lines 65-106* |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)  
See pages 4-5, lines 108-124 |
| --- | --- | --- |
| METHODS |  | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review  
See page 6, lines 139-152 and page 7, line 169 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage  
See pages 6-7, lines 154-174 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated  
See Appendix 1 |
| Study records: Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review  
See page 7, line 171 |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)  
See page 7, lines 176-181 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators  
See page 8, lines 184-189 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications.  
See Appendix 2 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale  
See page 8, lines 191-202 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis  
See page 8, lines 188-189 |
Data synthesis

15a Describe criteria under which study data will be quantitatively synthesised

See page 9, lines 212-213

15b If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall’s $\tau$)

See page 9, lines 213-215

15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)

See pages 9, lines 217-223

15d If quantitative synthesis is not appropriate, describe the type of summary planned

See page 9, lines 207-211

Meta-bias(es)

16 Specify any planned assessment of meta-bias(es)

See page 9, lines 223-224

Confidence in cumulative evidence

17 Describe how the strength of the body of evidence will be assessed (such as GRADE)

See page 9, lines 224-225

*It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shkekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.
Appendix 2. Example of the search strategy for Medline

1. exp Acidosis/ci
2. exp Acute Kidney Injury/
3. (Blood Urea Nitrogen/ or Reperfusion Injury/ or (cardiogenic adj shock*).tw,kf. or (critical* adj (care or ill* or patient*)).mp. or icu.tw,kf. or intensive care.mp. or (isch?emi* adj (reperfusion or injur*)).tw,kf. or life-threatening.mp. or ((multi* organ or multiorgan) adj (failure or dysfunction or dysfunction*)).mp. or polyangitis.mp. or polyarteritis.mp. or polyarteritis.mp. or rhabdo-myolysis.mp. or rhabdomyolysis.mp. or sepsis.mp. or septic.mp. or thrombo-cytopeni*.tw,kf. or thrombocytopeni*.tw,kf. or tubular cell*.tw,kf. or vasculit*.mp. or wegener* granulomatosis.mp.) and ((creatinin$ or de-hydrat* or dehydrat* or dialysis or kidney or renal).mp. or ur?emi*.tw,kf.)
4. *Hemolytic-Uremic Syndrome/
5. *Hemorrhagic Fever with Renal Syndrome/
6. Kidney Cortex Necrosis/
7. exp Kidney Diseases/ci
8. (Kidney Diseases/ or glomerular filtration rate*.tw,kf. or isch?emi* reperfusion injur*.tw,kf. or (renal adj (dysfunction* or dysfunction* or failure or function or impairment or insufficienc*)).mp.) and (Acute Disease/ or Cardiovascular Diseases/ or exp *Cardiovascular Surgical Procedures/ or exp *Cardiovascular System/su or *Contrast Media/ or exp *Diagnostic Imaging/ or Ischemia/ or exp Neurologic Manifestations/ or exp Substance-Related Disorders/ or ci.fs. or cardiac surg*.mp. or cardio-pulmonary*.tw,kf. or cardiopulmonary.tw,kf. or cirrhosis.ti. or microangiopath*.tw,kf. or microangiopath*.tw,kf. or pre operative*.tw,kf. or preoperative*.tw,kf. or postoperative*.tw,kf. or post operative*.tw,kf. or postoperative*.tw,kf. or revers*.tw,kf.)
9. Nephritis, Interstitial/
10. Renal Insufficiency/
11. (acute adj2 (kidney or renal or nephr* or glomer* or h?emodialy* or dialysis)).mp.
12. aki.tw,kf.
13. anti gbm.tw,kf.
14. anuri*.mp.
15. (anti glomerular or antiglomerular).mp.
16. azotemi*.mp.
17. (glomerulonephritis.mp or nephrit*.tw,kf.) and ((acute or anca*).tw,kf. or crescentic.mp. or rapidly progressive.tw,kf)
18. h?emolytic ur?emi*.tw,kf.
19. hepatorenal syndrome.mp.
20. (impair* or improved or recover*) adj2 renal function).tw,kf.
21. (induced adj (kidney or renal)).tw,kf.
22. (interstitial or tubulointerstitial) adj nephr*.tw,kf.
23. (injur* or isch?emi* or reperfusion or contrast medi*).mp. and (renal tubul* or tubular).tw,kf.
24. ((kidney or renal) adj failure*).tw,kf.
25. (kidney or renal) adj injur*.tw,kf.
26. (kidney or renal) adj insufficienc*.tw,kf.
27. (kidney* or renal) adj isch?emi*).tw,kf.
28. (nephropath* and (cast or (contrast* adj (agent* or induced or medi*)) or crystal* or iodinated or radioccontrast*)).mp.
29. nephrotox*.tw,kf.
30. (obstruct* adj2 (kidney* or nephropath* or renal or uropathy)).tw,kf.
31. oliguri*.mp.
32. (pre renal or prerenal).tw,kf.
33. (renal adj (hypo perfusion or hypoperfusion)).tw,kf.
34. (renal adj2 thrombosis).tw,kf.
35. (thrombotic adj (thrombocytopeni* or microangiopathy)).tw,kf.
36. (tubul* adj (damage* or injur* or necrosis)).tw,kf.
37. (worsening and renal).tw,kf.
38. or/1-37 [Combined AKI MeSH & textwords - modified filter from Hildebrand 2014 doi:10.1093/ndt/gft531]
39. Automation/
40. Automation, Laboratory/
41. Biological Markers/ and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*).tw,kf.
42. Biomedical Technology/
43. exp Cell Phones/
44. Clinical Alarms/
45. Clinical Laboratory Information Systems/
46. Creatinine/bl and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*).tw,kf.
47. Decision Support Systems, Clinical/
48. Drug Therapy, Computer-Assisted/
49. exp Electronic Health Records/
50. Health Information Systems/
51. Hospital Information Systems/
52. Information Systems/
53. Management Information Systems/
54. Medical Informatics/
55. Medical Informatics Applications/
56. Medical Order Entry Systems/
57. Medical Records Systems, Computerized/
58. Medication Systems, Hospital/
59. Monitoring, Physiologic/is
60. Point-of-Care Systems/
61. Reminder Systems/
62. Software/ and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*).tw,kf.
63. User-Computer Interface/
64. (acute kidney injury network* or AKIN or AKI network*) and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*).tw,kf.
65. (alarm* and (automat* or comput* or digit* or e mail or electronic or email or software or sms or text*)).tw,kf.
66. (alert* and (automat* or comput* or digit* or e mail or electronic or email or software or system* or sms or text*)).tw,kf.
67. (app or application* or apps or phon* or smart phon* or smartphon* or telephon*) and (alert* or messag* or notif* or remind* or warn*).tw,kf.
68. automated system*.tw,kf.
69. ((bed side or bedside or electronic) adj2 system*).tw,kf.
70. computer assist*.tw,kf.
71. (comput* adj2 system*).tw,kf.
72. computerized decision support*.tw,kf.
73. (computerized adj2 order entr*).tw,kf.
74. CPOE*.tw,kf.
75. delta check*.tw,kf.
76. (e alarm* or e alert* or e notification* or e report* or e warning*).tw,kf.
77. electronic order entry system*.tw,kf.
78. (electronic adj2 (recogni* or report*)).tw,kf.
79. information system*.tw,kf.
80. (integrated adj2 system*).tw,kf.
81. ((KDIGO or kidney disease improving global outcomes) and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*).tw,kf.
82. (laborator* adj2 alert*).tw,kf.
83. (messag* and (automat* or comput* or digit* or e mail or electronic or email or software or system* or sms or text*)).tw,kf.
84. (monitoring adj2 (automat* or comput* or digit* or electronic or software or system*)).tw,kf.
85. (notif* adj2 (automat* or comput* or digit* or e mail or electronic or email or software or system* or sms or text*)).tw,kf.
86. pathology software.tw,kf.
87. (real time adj (alert* or notification*)).tw,kf.
88. (reminder* adj2 (automat* or comput* or digit* or e mail or electronic or email or software or sms or system* or
text*)).tw,kf.
89. ((RIFLE or risk injury failure loss) and (alarm* or alert* or information system* or messag* or notif* or remind* or
reporting system* or warn*)).tw,kf.
90. (serum creatinine and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system*
or warn*)).tw,kf.
91. surveillance system*.tw,kf.
92. (urinary output* and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system*
or warn*)).tw,kf.
93. (warn* adj2 (automat* or comput* or digit* or e mail or electronic or email or software or sms or text*)).tw,kf.
94. or/39-93 [Combined MeSH & textwords for e-alerts]
95. and/38,94 [Combined searches for AKI & e-alerts]
96. limit 95 to (english or french) [Language limit]
97. limit 96 to yr="1990-current" [Publication date limit]
98. remove duplicates from 97
Appendix 3. Proposed data variable for extraction.

| Data                | Description                                                                 |
|---------------------|-----------------------------------------------------------------------------|
| Author              | First author name                                                          |
| References          | Journal, Issue, volume, pages                                               |
| Impact factor       | Impact factor of the journal in the year published                         |
| Country             | Country in which the study was conducted                                    |
| Year                | Start and end date of study                                                 |
| Design              |                                                                             |
| Type                | RCT, quasi-RCT, before and after, observational [if observational what is the control group] |
| Blinding            | Is the study blinded and to who                                             |
| Allocation concealment | For RCT is the allocation concealment preserved                           |
| Number of centers   | Single-center, multi-center                                                 |
| Setting             | Ward, ICU, both                                                            |
| Inclusion criteria  | List all inclusion criteria of the study                                    |
| Exclusion criteria  | List all exclusion criteria of the study                                    |
| Study Quality       | See Appendix 2                                                              |
| Funding             | Industry vs. publicly funded vs. both                                       |
| Type of alert       |                                                                             |
| Threshold for activation | Criteria used to diagnose AKI (RIFLE, KDIGO, etc.)                      |
| What is the baseline creatinine used? | Definition of baseline creatinine                                     |
| How is a baseline creatinine value determined when none is available | Method by which a baseline creatinine is defined when none is available |
| Timing              | Instantaneous or batched alerts (frequency if batched)                     |
Appendix 3. Data to be collected in the form (continued)

| Data | Description |
|------|-------------|
| **Type of alert (continued)** |  |
| Target provider of alert | Physician/resident/associate/MRP/pharmacy/multiple |
| Training given to the caring team [i.e. any formation about AKI (diagnosis, investigations, management) given before the study by the research team to clinicians (attendings, residents, fellows, pharmacists or nurse practitioners) who will receive the alert] | Yes or no |
| **Method of communication** |  |
| Alert sent to the recipient | e-mail, page, call, text |
| Alert in patient’s EMR | Notification (text), red flag |
| **Mechanism of alert generation** |  |
| Where is it detected? | EMR, dedicated alerting system, biochemistry LIMS |
| Automation | Automated or semi-automated |
| What is generated | Message or call or both |
| Degree of intrusiveness | See Appendix 4 |
| **Content** |  |
| Integrated clinical decision support | Yes or no |
| If integrated clinical decision support, *how* is it integrated? | Integrated in the message of the alert or alert provide a link (to recommendation) or verbal opinion by member of the search team |
| If integrated clinical decision support, *what* is included? |  |
### Appendix 3. Data to be collected in the form (continued)

| Content (continued)                          | Description                                      |
|---------------------------------------------|--------------------------------------------------|
| **Diagnostic**                              | Urinalysis, ultrasound                           |
| **Monitoring**                              | Repeat creatinine [if provided, when], u/o measurement |
| If integrated clinical decision support, *what is included?* (continued) | medication list review, nephrotoxins to avoid [including contrast], drugs dose adjustment, direct a consult with a specialist [either nephrology or ICU] |
| **Mechanism of harm avoidance**             | Is the clinical decision support generic (ex. Click here to order a urinalysis) or context specific (ex. The patient is taking gentamicin click here to d/c the medication) |
| **Degree of intelligence of clinical decision support** | | |
| If AKI progress is there another alert generated | Yes or no |

### Outcomes measured in the study

| Process outcomes                           | Yes or no |
|--------------------------------------------|-----------|
| **Time to drugs adjustment**               |           |
| **Chart documentation of AKI**             |           |
| **Medication list revision**               |           |
| **Patients who received a nephrotoxin**    |           |
| **ICU or nephrology consult**              |           |
| **Follow-up creatinine**                   |           |
Appendix 3. Data to be collected in the form (continued)

| Data | Description |
|------|-------------|
| **Outcomes measured in the study (continued)** |  |
| Any investigation (ultrasound or urinalysis) | Yes or no |
| Use of fluid, diuretics or vasopressor | Yes or no |
| **Patient-centered outcomes** |  |
| Receipt of RRT | Yes or no |
| Creatinine [peak creatinine, % progression creatinine, % patients whose creatinine progress, % patients who progress to stage 3 AKI by KDIGO or stage F by RIFLE, recovery] | Yes or no |
| Death [either ICU, 7-day, hospital, 30 days, long-term [however defined]] | Yes or no |
| **Health resources use** |  |
| ICU admission | Yes or no |
| ICU readmission | Yes or no |
| ICU length of stay | Yes or no |
| Hospital length of stay | Yes or no |
| **Results** |  |
| Patients related data |  |
| Number | Total number of patients included |
| Age (mean [SD]) |  |
### Appendix 3. Data to be collected in the form (continued)

| Data                                      | Description                                      |
|-------------------------------------------|--------------------------------------------------|
| **Results (continued)**                   |                                                  |
| % male                                    |                                                  |
| CKD status                                | As percentage                                   |
| Baseline creatinine                       | In umol/L                                        |
| Enrolment creatinine                      | In umol/L                                        |
| Diagnostic                                | Medical/surgical/cardiac surgical                |
| Process outcomes [as stated above]        | All value related to process outcomes entered separately to be analyze in meta-analysis |
| Clinical outcomes [as stated above]       | All value related to clinical outcomes entered separately to be analyze in meta-analysis |
| Health services use [as stated above]     | All value related to health services use entered separately to be analyze in meta-analysis |
### Appendix 4: Study Quality Assessment - Modified Downs and Black Score (14)

| Criteria                                                                 | Score               |
|-------------------------------------------------------------------------|---------------------|
| **Reporting**                                                           |                     |
| Is the hypothesis/aim/objective of the study clearly described?         | No = 0 ; Yes = 1    |
| Are the main outcomes to be measured clearly described in the Introduction or Methods section? | No = 0 ; Yes = 1    |
| Are the characteristics of the patients included in the study clearly described? | No = 0 ; Yes = 1    |
| Are the main findings of the study clearly described?                   | No = 0 ; Yes = 1    |
| Does the study provide estimates of the random variability in the data for the main outcomes? | No = 0 ; Yes = 1    |
| Have all important adverse events that may be a consequence of the intervention been reported? | No = 0 ; Yes = 1    |
| Have the characteristics of patients lost to follow-up been described?  | No = 0 ; Yes = 1    |
| Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001? | No = 0 ; Yes = 1    |
| **External validity**                                                   |                     |
| Were the subjects asked to participate in the study representative of the entire population from which they were recruited? | No = 0 ; Yes = 1    |
| Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? | No = 0 ; Yes = 1    |
| **Internal validity – bias**                                            |                     |
| If any of the results of the study were based on “data dredging”, was this made clear? | No = 0 ; Yes = 1    |
| In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients? | No = 0 ; Yes = 1    |
| Were the statistical tests used to assess the main outcomes appropriate? | No = 0 ; Yes = 1    |
| Was compliance with the intervention/s reliable?                        | No = 0 ; Yes = 1    |
| Were the main outcome measures used accurate (valid and reliable)?      | No = 0 ; Yes = 1    |
| **Internal validity - confounding**                                     |                     |
| Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? | No = 0 ; Yes = 1    |
| Were losses of patients to follow-up taken into account?                | No = 0 ; Yes = 1    |
| Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? | No = 0 ; Yes = 1    |
| **Disclosure**                                                          |                     |
| Was funding disclosed?                                                  | No = 0 ; Yes = 1    |

**Overall Quality**
- 13-19 = good
- 7 – 12 = moderate
- <7 = poor
# Appendix 5. Degree of intrusiveness gradation system

| Grade | Level of Disruptiveness | Description | Generic Example |
|-------|--------------------------|-------------|-----------------|
| 1     | Passive                  | An alert is generated and displayed in the EMR/CIS. This alert does not disrupt provider workflow or require acknowledgement. | A patient fulfills criteria for KDIGO AKI stage 2 in the EMR/CIS. The following alert is generated and displayed:  

*AKI stage 2* |
| 2     | Active                   | An alert is generated and displayed in the EMR/CIS or a phone call is given to the attending physician. This alert is disruptive. This could be in the form of a specific alert [pop-up] window or flashing alert within the EMR/CIS. This alert could also generate a page, mobile text and/or email of the alert or can be a verbal notification from the lab to the most responsible provider (MRP).  

When electronic, this alert does not require acknowledgement. When it is a phone call, no repeat call is scheduled | A patient fulfills criteria for KDIGO AKI stage 2 in the EMR/CIS. In addition to the passive alert, the following alert is generated and sent to the MRP's pager, mobile, and/or email:  

*Patient XX has developed AKI stage 2* |
| 3     | Disruptive               | An alert is generated and displayed in the EMR/CIS. This alert has a higher level of disruptiveness. This could be in the form of a specific alert [pop-up] window or flashing alert within the EMR/CIS and will generate a page, mobile text and/or email to notify the most responsible provider (MRP) of the alert.  

This alert will require acknowledgement in the EMR/CIS. Serial repeat pages, mobile texts and/or emails alerts are generated at fixed times until the alert is acknowledged in the EMR/CIS. The alert may also not disappeared until a positive action (ex. completing a care bundle) has been undertaken. | A patient fulfills criteria for KDIGO AKI stage 2 in the EMR/CIS. In addition to the passive/active alert, the following alert is generated and sent to the MRP's pager, mobile, and/or email:  

*Patient XX has developed AKI stage 2. To avoid additional alerts, this must be confirmed in the patient's EMR.* |
### Appendix 5. Degree of intrusiveness gradation system (continued)

| Grade | Level of Disruptiveness | Description | Generic Example |
|-------|-------------------------|-------------|-----------------|
| 4     | Very disruptive         | An alert is generated and displayed in the EMR/CIS. This alert has the highest level of disruptiveness to workflow. This alert would have similar form to the above alerts; and will directly disrupt EMR/CIS activities, require acknowledgement and specific actions prior disarming. | A patient fulfills criteria for KDIGO AKI stage 2 in the EMR/CIS. In addition to the passive/active alert, the following alert is generated and sent to the MRP’s pager, mobile, and/or email:  

Patient XX has developed AKI stage 2.  

Proposed [action] cannot be performed because [AKI risk modification].  

Clinical Decision Support: do not [administer nephrotoxin] due to risk of worsening AKI; consult nephrology. |