Author's response to reviews

Title: The Effectiveness of Computerized Order Entry at Reducing Preventable Adverse Drug Events and Medication Errors in Hospital Settings: A Systematic Review and Meta-Analysis

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Author's response to reviews: see over
February 21, 2014

Dear Systematic Reviews Editorial Team,

Thank you very much for the opportunity to revise the attached manuscript, “The Effectiveness of Computerized Order Entry at Reducing Preventable Adverse Drug Events and Medication Errors in Hospital Settings: A Systematic Review and Meta-Analysis.”

Below you will find point-by-point responses to reviewer comments and editorial requests.

Please let us know if we may provide additional information of potential use.

Sincerely,

Teryl K. Nuckols, MD, MSHS
Title: The Effectiveness of Computerized Order Entry at Reducing Preventable Adverse Drug Events and Medication Errors in Hospital Settings: A Systematic Review and Meta-Analysis

Reviewer 1

Version: 2
Date: 22 January 2014
Reviewer: Jennifer R Bellis

Reviewer's report:

- The Title & Abstract accurately convey the reported findings of the study.
- The question is well-defined and justified - it makes sense to evaluate the impact of CPOE on errors which lead to harm, rather than just errors per se.
- The paper is very well written and easy to read.
- The systematic review methods are clearly described.

Discretionary Revisions

- In the introduction you state that errors in timing are generally less risky than giving a drug to the wrong patient - a justification of this statement is needed either by providing an example or a reference to support it.

  o Response: Thank you for this suggestion; we have added a clinical example.

- Methods - Since you developed and used your own search strategies, could you comment on whether you think it is it possible that a search of databases for primary studies published prior to January 1, 2007 may have identified additional studies not found by previous reviews? A statement to justify your approach could be added to the discussion.

  o Response: We have added a couple of sentences to the limitations section addressing this issue.

- You elected to conduct a subgroup meta-regression analysis with year of publication as a predictor - using the year the study was conducted would make more sense because time to publication for each study will have varied. Please consider updating this.

  o Response: We agree, and would have looked at the year that CPOE was implemented, if feasible. This information, as well as when data were collected, was missing from about half the studies. A sentence in the second paragraph on page 10 (methods section, now highlighted in yellow) mentions this issue. We have added a parenthetical statement at the bottom of page 13 (results section) that also includes this information.
Minor Essential Revisions

- Footnotes are provided in the legend for Figure 1 (PRISMA flow diagram) but the symbols do not appear in the flow diagram - please update.
  
  o **Response:** Thank you for detecting this issue. We moved the footnote material to the relevant paragraph on page 7, paragraph 1. These footnotes went with a previous version of the flow diagram and are no longer relevant.

- Results - the medication error rate in the text for Van Doormal et al. (Ref 67) does not match that in Table 1 - please correct.
  
  o **Response:** Thank you also for catching this error. We have corrected the text on page 11 para 3.

Major Compulsory Revisions

- In the discussion you state that the baseline rate of hospitalizations associated with medication errors was significantly associated with effectiveness of CPOE. Can you comment on why the range of baseline medication error rates is so wide?
  
  o **Response:** There are three potential reasons that baseline error rates may have varied so greatly across the studies: (1) definitions of errors varied, (2) methods for detecting errors varied, and (3) rates of errors varied. We attempted to reduce the first two sources of variability but are unlikely to have completely eliminated them.

  - We applied a uniform definition of errors when selecting events to include, yet studies (and even individual reviewers) are likely to operationalize the concept of medication error somewhat differently.

  - To limit variability due to detection methods, we required that methods be described and that incident reporting not be the sole method of detection (it is not a valid method for detecting events, as we explain to the second reviewer below). Nonetheless, as seen in Table 1 and Appendix Table 4, methods of detection did vary across the studies. We tested whether event detection methods were associated with effectiveness and found that they were not.

  - Finally, rates of errors do vary across hospitals. Hug et al. (citation 12) measured medication error rates at six community hospitals. Across the sites, rates per 100 patient days ranged from 29 to 86, or 25 to 57% of hospitalizations. They used multiple complementary methods to detect events. This research team includes national experts in studying medication errors and their research methods appear to have generally been of the highest quality possible for this field, so event definitions were likely applied consistently.

  - We have added a sentence to the results section (p 11, para 3) to better acknowledge that event definitions and detection methods varied across studies. This is in the same paragraph where the variability in baseline error rates is described.
It is my understanding, from your description of methods for data extraction (page 8), that these rates are for errors which caused harm or had the potential to. Did the studies and subsequently the review team use a consistent approach to determine whether errors had the potential to cause harm?

- **Response:** As you note, our objective was to focus on higher risk errors—but we did not mean to suggest we were focusing on only the errors that pose the highest risk. Rather, we sought to study errors that involve relatively higher risk, and have excluded those with very low risk. It would be hard to argue that any error poses zero risk. We have changed the wording slightly in hopes that this nuance will be clearer.

- The review team created a definition of error with the potential to cause harm and multiple reviewers applied it consistently to the information available from each study. However, as noted above, the definitions of events and detection methods varied across studies, and some studies provided limited detail about the degree of risk associated with the errors detected. Several studies used the NCC MERP (http://www.nccmerp.org/) categories for classifying errors, but many did not. See Appendix Table 3 and the paragraphs preceding it for specific details on the information extracted and which subtypes of errors were included from each study.

- It might be useful to the reader if you indicate exactly which errors were included in the data extraction as well as which were not e.g. dose errors with potential for harm included, omission of patient ward excluded.

- **Response:** We wholeheartedly agree that this information is useful. Perhaps you did not receive the Appendix because it contains this information itemized for each study (see Table 4). There is too much variability to include these details in the main manuscript.

- According to Table 1, in some of the studies almost 100% of admissions were subject to a medication error. This seems like an extremely high rate if only errors causing harm/with the potential to cause harm were included. Can you comment on why it is so?

- **Response:** As noted above, rates of medication errors do vary widely even when event definitions and detection methods are held constant. The observed variability in event definitions and detection methods would increase this further.

- Towards the end of your discussion you state that a potential explanation for increases in medication errors with CPOE in two of the included studies is that the CPOE systems may have increased medication errors at lower risk for causing ADEs. This explanation does not seem to align well with your approach to data collection which sought to exclude errors at low risk of causing harm.

- **Response:** The risk posed by errors varies greatly, and depends on several factors, including the nature of the medication (e.g., chemotherapy vs. stool
softener), the type of error (e.g., timing vs. wrong patient), and the vulnerability of the victim (e.g., ICU patient with multi-organ failure vs. young healthy adult with a skin infection). We sought to eliminate errors that had a particularly low probability of causing harm, as described in the Methods (page 8, para 3) and Appendix. Some of the events we excluded, such as the disallowed abbreviations, illegible prescriptions, and disallowed drug names no longer occur when CPOE is being used because providers generally select medications, doses, frequencies, etc. from pick lists or pull-down menus. Including these low risk events would have biased findings in favor of CPOE.

- As an example, using a disallowed medical abbreviation increases the chance that the pharmacist or nurse will misread the order and dispense or administer the wrong thing. However, these abbreviations are well known, and, if legible, easily understood. In case of doubt, standard practice is for the pharmacist or nurse to call the physician for clarification. While using disallowed abbreviations is no longer accepted practice, the probability that a patient would be harmed by any given use of a disallowed abbreviation is low.

- While we attempted to eliminate the errors that were particularly unlikely to cause harm, we did not attempt to eliminate all errors at relatively lower risk of causing harm.

- Both of the studies that saw increases in medication errors used relatively rigorous methods for defining and detecting errors, and the increases do not appear due to inconsistency in research methods between the study periods. See Appendix Table 3. Nonetheless, another possibility is that CPOE could have made it easier to detect certain errors. We have added a sentence making this point on page 16, paragraph 1.
Reviewer 2

Version: 2
Date: 21 February 2014
Reviewer: Elizabeth Conroy

Reviewer's report:

Major Revisions

• METHODS - Study Selection - First paragraph - ‘we excluded studies that did not describe the methods for detecting medication events, or that used in incidence reporting...’. This exclusion criteria needs further justification – seems to me that there is the potential to exclude studies that are potentially relevant under this current criteria.

• Could authors not be contacted to ask for details about the methods of detection –some attempt should at least be made rather than automatic exclusion.

• Excluding studies simply because they use incidence reporting (small % of events) may bias your results. The whole purpose of meta-analysing data is to pool together and make inference about a collection of studies that attempt to answer the same question – one of the main benefits of meta-analysis is to pool together results from similar studies, when the individual studies contain small events which may otherwise be difficult to draw any concrete conclusions from individually.

  o Response: We appreciate the reviewer’s concern about the possibility of excluding relevant studies. To clarify the term of interest, it is incident reporting. It does not measure the incidence of medication errors or patient safety events. Rather, incident reporting is a specific practice in hospitals and health systems through which front-line providers, generally nurses, voluntarily report events during which patients were harmed or could have been harmed. The reports are generally reviewed by both hospital risk managers and quality improvement leaders and changes in protocols, etc. may be made on this basis.

  o While incident reporting is a useful method for obtaining qualitative data about risks in an institution, it is not a valid method for quantitative analyses, for two reasons. First, it has been shown to detect only 0.2% to 6% of patient safety events such as medication errors (see Flynn et al. 2002 cited in paper as well as Murff et al., “Detecting adverse events for patient safety research: a review of current methodologies” Journal of Biomedical Informatics, 2003). Such low detection rates mean that the vast majority of medication errors are missed.

  o Second, incident reporting is voluntary and it is widely recognized that rates of reported incidents are at least as influenced by providers’ motivations to report as they are by the underlying incidence of reportable events. Any number of factors can affect provider motivation, such as encouragement by hospital leadership, improved attention to the safety issues that are identified through reporting --or perhaps even satisfaction with a new CPOE system. Reporting
medication errors more or less often could be a passive way that staff might show their approval or disapproval of such a system.

- Given that incident reporting detects so few events and varies for reasons unrelated to the occurrence of medication errors, studies that relied wholly on this method do not meet a minimum threshold for validity.

- In addition, event rates measured solely through incident reporting are sufficiently different from event rates measured through more comprehensive and rigorous means that pooling the two types of studies did not seem justifiable.

- We did not exclude studies that used incident reporting as one of multiple techniques for detecting events, since the number of events detected through other means would dwarf those detected through incident reporting.

- As to studies that did not describe methods for event detection, we agree that contacting each author would be one approach to addressing this issue. In the 16 years experience of the RAND Evidence-Based Practice Center, response rates to such requests have generally been poor. Given its importance, we considered describing the event detection methods to be a minimum criterion for study quality.

- We now specify detection rates for incident reporting on page 8, paragraph 1. We have added a sentence to the limitations that mentions our exclusion of studies that used incident reporting or that did not report event detection methods.

Minor Essential Revisions

- **ABSTRACT** – Conclusions - Too brief - does not report limitations or implications of findings.
  - We have added additional information to the abstract, mentioning limitations (weak study designs) as well as implications for policy.

- **METHODS** – Data Sources and Searches – Second paragraph - ‘hand searched nine websites…and bibliographies of other publications know to us’. For transparency and replication of current work, these websites and publications should be referenced.
  - **Response:** We have added the list of websites to the paragraph.

- **PAGE 9** –‘equaled’ should be ‘equalled’
  - **Response:** Thank you for your attention to detail but the spell checker for Microsoft Word respectfully disagrees. Perhaps this is a difference in spelling style due to language use in different countries.

- **METHODS** – Data extraction and quality assessment – Third paragraph – Not clear how CDSS sophistication is defined. The levels of basic, moderate and advanced seem quite
arbitrary. Was this determined by original authors or following some sort of definition? This should be described.

- **Response:** This was not clear in the text, thanks for pointing that out. Please refer to the footnote in Table 1, which provides brief definitions and cites a paper from which the definitions were drawn. We have added a mention of this Table to the paragraph.

- **METHODS – Data Synthesis and Analysis – First paragraph** - ‘if a study provided more than one unit of exposure, we select the unit most commonly reported across studies’. This needs some careful consideration. Different units of exposure will often lead to a different interpretation. For each different exposure used across the studies, what question is answered? You need to present the data on all possible exposures or at least those that are meaningful, not just the ones that was reported most frequently.

  - **Response:** We completely agree that this is an important consideration. We examined all possible units of exposure and tested whether the selection of units affected results. This is stated on page 10 paragraph 2 and page 13 paragraph 2 (now highlighted for ease of detection). Results were not affected by the units of exposure.

- **METHODS – Data Synthesis and Analysis – Second paragraph** - We usually specify the test of heterogeneity not homogeneity.

  - **Response:** We have changed the term to heterogeneity.

- **METHODS – Data Synthesis and Analysis – Second paragraph** - ‘We report the I2 statistic unless the two results conflict’. Methodologically this sounds weak – I would re-phrase. The decision is often subjective. For the Q-stat we often use p>0.1 not 0.05.

  - **Response:** We deleted this sentence because we have actually already reported the Q-statistic in Figures 2 and 3.

- **RESULTS - Intervention, contextual and methodological factors needs to be indicated as subsection. This section does not quantify results or reference figure. Results relating to the factors investigated are not supported numerically.**

  - **Response:** There was a subsection headed “Intervention, Contextual, and Methodological Factors” (top of page 14). We changed this to “Intervention Design and Implementation, Contextual, and Methodological Factors” to better match Figure 3, and we added a similar subsection to the Methods section.

  - **Response:** We have added a reference to Figure 3 to the first paragraph on page 14.

  - **Response:** We have added the numerical information to the results addressing the various factors.

- **FIGURE 1 - include removals at all stages of flow. For example, number of duplicates and also reasons for the three studies not included in meta-analysis though included in qualitative analysis so that this figure is stand alone.**
Response: We are uncertain how to respond to this comment since the journal has a standard flow diagram that they require authors to use. We simply filled in the boxes within that flow diagram; it did not have a box for duplicates or a box explaining why studies were excluded from meta-analysis.

- No assessment of risk of bias or methodological quality was performed on any of the included studies. This is an important component of a review so that authors/readers can report on how the methodological limitations may affect their overall conclusions. While standard tools may not be fit for purpose for this particular review, it is common for review authors to develop a way to assess the quality of studies using items that they think are considered to be important.

  Response: We completely agree methodological quality is important. The previous version of our article did not provide that information in a very accessible manner.

  We applied minimum quality criteria when selecting studies (i.e., excluded studies that compared event rates in dissimilar units, did not report event detection methods, etc.).

  As stated on page 9, third paragraph (now highlighted in yellow), we adapted relevant reporting criteria from SQUIRE and obtained information related to study quality such as study design, training of reviewers, blinding, and reliability assessment as well as funding source. The information could take up a lot of space, so we attempted to consolidate it via a footnotes in the last column in Table 1 (e.g., R = reliability, B = blinding, now highlighted in yellow).

  To make this information more accessible, we have added it to a new table in the Appendix as well as information on funding source so that it is easier to read.

METHODS – Study Selection – First paragraph - Not convinced that paediatric studies should have been excluded. While they may contribute a smaller number of hospitalised patients they are arguably still an informative and important subgroup. Were any of the excluded or included studies a mixed population?

Perhaps include a paediatric analysis as a recommendation for further research and build upon argument for exclusion.

  Response: We do not mean to suggest that children are unimportant. Rather, they differ from adults, especially older adults, in terms of their vulnerability to medication errors. Dosing by weight is a unique issue for children, for example. There are not many children in hospitals but there are numerous adults over age 65, who have a different set of risk factors. Elderly adults have reduced abilities to metabolize medications due to age-related declines in liver and kidney function, as well as a larger number of co-morbid illnesses. Consequently, based on the differences between pediatric populations and elderly adults, pooling pediatric and adult studies did not appear appropriate.
Some of the studies we included implemented CPOE hospital-wide and did not break out results by age, so yes, there were mixed populations. Given children tend to comprise only 6% of the hospitalized population, this is unlikely to have affected results.

Previous systematic reviews have examined the effects of CPOE in pediatric populations specifically. To the limitations, we have added a recommendation to have future investigators conduct a meta-analysis in pediatric populations.
Editorial request:

- Please include a Conclusions section as the last section of the text. This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance.
  
  o Response: We have created a separate conclusion and expanded the discussion of importance and relevance.

- Can you please confirm that each author meets the authorship criteria below:
  - Substantial contributions to: the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND - Drafting the work or revising it critically for important intellectual content; AND - Final approval of the version to be published.
  
  o Response: We have revised the authorship statement according to the instructions and example.

- We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

- Please also highlight (with 'tracked changes'/coloured/underlines/highlighted text) all changes made when revising the manuscript to make it easier for the Editors to give you a prompt decision on your manuscript.

- Please also ensure that your revised manuscript conforms to the journal style (http://www.systematicreviewsjournal.com/info/instructions/). It is important that your files are correctly formatted.