PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Computerized decision to reduce inappropriate medication in the elderly: A systematic review with a meta-analysis protocol
AUTHORS	Monteiro, Luís; Maricoto, Tiago; Solha, Isabel; Monteiro-Soares, Matilde; Martins, Carlos

VERSION 1 – REVIEW

REVIEWER	Dr Tau Ming LIEW 1) Institute of Mental Health, Singapore 2) Saw Swee Hock School of Public Health, National University of Singapore
REVIEW RETURNED	15-Aug-2017

GENERAL COMMENTS	This is a protocol for systematic review and meta-analysis on whether computerized decision can help to reduce adverse outcomes related to inappropriate medication in elderly. This topic is relevant because inappropriate prescribing is not uncommon in elderly and has previously been associated with adverse outcomes. Moreover, inappropriate prescribing is potentially preventable. Hence, there is a role to review whether newer technologies such as computerized decision help to improve outcome. The authors has not mentioned two recently conducted systematic review similar to theirs (please see https://www.ncbi.nlm.nih.gov/pubmed/27321600 and https://www.ncbi.nlm.nih.gov/pubmed/22592727), and how their current systematic review can add value to the literature. In my opinion, the value of the current systematic review seems to lie in the conduct of meta-analysis, which has not previously been done. There are a number of concerns which I will like to highlight below: 1) Eligibility criteria (page 5, line 117): the authors did not seem to limit the language of publication. Does that mean they are prepared to analyse the results even if the language of publication is not familiar to the authors? 2) Information sources (Page 5, line 121): In the abstract, “Web of Science” was mentioned as one source of information. However, it was no longer mentioned in the Methods section. The authors may need to correct this conflict 3) Search Strategies (Page 5, line 135): The search strategies may not be sufficient and may be overly simple. Use of [Mesh] terms alone may miss out more recent publications.

	Hence, it may be useful to include keywords as well. If available, it may also be useful to include any proprietary names of computerized decision support system that the authors may be aware of. 4) Data items (Page 6, line 162): Among the many outcomes that have been listed, it may be useful to specify the outcome that the authors will give priority to. Hospitalization may also be an important outcome that has not been stated by the authors. 5) Data synthesis (Page 6, line 176): The authors stated that they will use “fixed-effect model” if “tests for heterogeneity are not significant”. That may not be a sufficiently good reason to choose the fixed effect model instead of the random model (unless the authors have sufficiently strong reason to justify that the studies are nearly identical). 6) Subgroup analysis (Page 7, line 183): It may be useful to pre-specific any subgroups that may be relevant and of interest to explore further. The authors may want to consider conducting meta-regression to evaluate whether the covariates have significant influence on the heterogeneity. 7) Reporting bias (Page 7, line 188): The authors may want to consider including funnel plot and statistical tests in the assessment of reporting bias. 8) Randomized studies (Page 7, line 201): It was not clear why the authors decided to use “generic inverse variance” in the presence of cluster-randomization method. 9) Dichotomous data (Page 7, line 205): It may not be necessary to exclude data just because there were zero events. The authors may want to consider using zero-cell correction methods – please refer to the Cochrane Handbook for more details and references. 10) Discussion (Page 8, line 208): The authors may wish to consider mentioning any limitations of this systematic review? On the whole, this is a useful research especially in meta-analysing the effect size of computerized decision (a current gap in the literature). However, the planned meta-analyses may need to be improved to capitalize on the strength of the research.

REVIEWER	Kjell H. Halvorsen UiT The Arctic University of Norway
REVIEW RETURNED	18-Aug-2017

GENERAL COMMENTS	Thanks for the opportunity to review this protocol article. I have some adressing comments that hopefully could raise the quality of the manuscript. 1. Keywords; there is a mismatch between keywords given in after the abstract and in the submitting scheme. I would belive that potentially inappropriate medicines could be included. 2. Maybe it is a formatting problem, but some of the words are merged togheter. 3. Line 98-100 can you please give examples of opportunities and barriers along with references?

	4. Line 101-103 does not make sense; please rephrase or elaborate 5. I don't think that we will be able to eliminate inappropriiate prescribing; but the purpose of computerised decision support system is to reduce PIMs, and increase omitted drugs. 6. You state in your aim "in terms of health outcomes"; are there any specific outcomes that you have in mind; or that you (from the litterature) are aware of? 7. In the paragraph concerning data synthesis you state that you will present "the range of clinical decision support"; I don't think this is in accordance to your aim. 8. PubMed is not a database...but a search engine... Medline is... Have you considered to include ISI web of science? 9. You state in the discussion section that this review "will help identify the best decision support available, as well as it limitations"; I'm not sure if I agree that by doing this review you will be able to do so; computerised decision systems and how easily they integrate with other softwares would, from my point of view, determine the success of such tools, at least, to a certain extent. Good luck with conducting the review.

REVIEWER	Ben Schöttker German Cancer Research Center (DKFZ) Germany
REVIEW RETURNED	23-Aug-2017

GENERAL COMMENTS	1. The population of interest should be described in more detail: Do the authors plan to include trials conducted with the general older population or with older adults with particular diseases? Also, the authors should explain how potentially inappropriate medications/prescriptions are defined. Furthermore, it is not clear, if the systematic review focuses on the reduction of potentially inappropriate medications (line 63) or on the decrease of potentially inappropriate prescriptions (line 104). Usually, these terms are not used synonymously. 4. The exclusion/inclusion criteria for the study selection process should be reported in more detail. The search strategy is not thorough enough: For example, the search in the pubmed database only consist of (three) mesh-terms. Consultation with a professional (e.g., a librarian) is recommended. Also, cross-referencing should be performed. In lines 150,151 the authors declare the use of data sheets. However, they do not describe the development or the contents of these sheets any further. The authors plan to perform a risk of bias assessment. However, they do not state how they plan to use this information in the data synthesis. The results could be used to perform sensitivity analyses by excluding those studies with high risk of bias. 6. The authors should define the outcomes more detailed. It is not clear, if the authors plan to examine all possible clinical outcomes or

	only certain ones. Also, the authors should define the primary endpoint (reduction of potentially inappropriate medication?) and the secondary endpoint. 7. The authors plan to decide on the random or fixed effects model based on the statistically calculated heterogeneity (see lines 171, 172, 176, 177). This should not be done. According to the Cochrane Handbook for Systematic Reviews of Interventions, the decision should be made in advance to the analyses, based on clinical assumption or the study situation. Furthermore, the authors report the statistical methods to be used in a rather general manner (compare lines 174,175). 8. The authors make statements without providing any references for proof (e.g., lines 89, 94, 100). Furthermore, the authors cite at least one incorrect reference (see line 97). The correct reference is the following: Reeve E, Gnjidic D, Long J, Hilmer S (2015) A systematic review of the emerging definition of "deprescribing" with network analysis: implications for future research and clinical practice. Br J Clin Pharmacol. 2015; 80(6):1254–1268) 13. The PRISMA checklist is incomplete: The authors did not choose Yes or No for the items 4, 5c, 6, 7, and 9 to 17. Furthermore, some of the line numbers are obviously incorrect (e.g., #12, #15c, #16). 15. The text contains a lot of typing errors and spelling mistakes. Some sentences are unintelligible. Also, there are incoherent sentences, especially in the abstract and introduction, and an inconsistent choice of wording (e.g. pubmed - MEDLINE). Revision by a native speaker is strongly recommended.

REVIEWER	Nicole Brandt, PharmD, MBA Peter Lamy Center on Drug Therapy and Aging, University of Maryland School of Pharmacy Baltimore, Maryland USA
REVIEW RETURNED	25-Aug-2017

GENERAL COMMENTS	Believes this is more of a framework for a systematic review vs the actual review.

VERSION 1 – AUTHOR RESPONSE

Reviwer#1

The authors has not mentioned two recently conducted systematic review similar to theirs (please see https://www.ncbi.nlm.nih.gov/pubmed/27321600 and https://www.ncbi.nlm.nih.gov/pubmed/22592727).
We thank you for this suggestion. We added the reference to these two articles and the following sentence:
“Other studies have addressed this issue (9, 13). Our study will include meta-analysis, which has not previously been done.”

1) Eligibility criteria (page 5, line 117): the authors did not seem to limit the language of publication. Does that mean they are prepared to analyse the results even if the language of publication is not familiar to the authors?

Response: We thank you for this remark. We will first contact the authors to ascertain if main data is available on other language and seek to translate whenever necessary. We have added this information on the manuscript:
“The search will be performed in January and February 2018. The search will have no language restrictions. We will first contact the authors to ascertain if main data is available on other language and seek to translate whenever necessary. A second search, using all identified keywords and proprietary names of computerized decision support system will then be undertaken across all included databases.”

2) Information sources (Page 5, line 121): In the abstract, “Web of Science” was mentioned as one source of information. However, it was no longer mentioned in the Methods section. The authors may need to correct this conflict

Response: We thank you for this comment. We will include the ISI Web of science in our search.

3) Search Strategies (Page 5, line 135): The search strategies may not be sufficient and may be overly simple. Use of [Mesh] terms alone may miss out more recent publications. Hence, it may be useful to include keywords as well. If available, it may also be useful to include any proprietary names of computerized decision support system that the authors may be aware of.

Response: We thank you for this suggestion. We added the reference to keywords and to any proprietary names of computerized decision support system.
“For MEDLINE, the query will be "Medical Informatics Applications"[Mesh] AND ("Deprescriptions"[Mesh] OR "Inappropriate Prescribing"[Mesh]) "decision support systems, clinical"[MeSH Terms] OR clinical decision support systems [Text Word] / "decision making, computer-assisted"[MeSH Terms] OR computer assisted decision making[Text Word] / "medical order entry systems"[MeSH Terms] / "medication errors"[MeSH Terms]; and for EMBASE ('medical informatics'/exp OR 'mobile application'/exp) AND ('deprescription'/exp OR 'inappropriate prescribing'/exp).
Reference lists will be checked in order to identify additional relevante studies to be included in the systematic review.

For ISI Web of science the query will be "Medical Informatics Applications"[Mesh] AND ("Deprescriptions"[Mesh] OR "Inappropriate Prescribing"[Mesh]) "decision support systems, clinical"[MeSH Terms] OR clinical decision support systems[Text Word] / "decision making, computer-assisted"[MeSH Terms] OR computer assisted decision making [Text Word] / "medical order entry systems"[MeSH Terms] / "medication errors"[MeSH Terms].”

4) Data items (Page 6, line 162): Among the many outcomes that have been listed, it may be useful to specify the outcome that the authors will give priority to. Hospitalization may also be an important outcome that has not been stated by the authors.

Response: We thank you for your comment. We added the following phrase:
“The authors will give priority to the following outcomes, by order of importance: mortality, hospitalization, any reported adverse drug withdrawal effects and quality of life measurement.”

5) Data synthesis (Page 6, lime 176): The authors stated that they will use “fixed-effect model” if “tests for heterogeneity are not significant”. That may not be a sufficiently good reason to choose the fixed

effect model instead of the random model (unless the authors have sufficiently strong reason to justify that the studies are nearly identical).
We thank you for this suggestion. We changed the model to random model.

6) Subgroup analysis (Page 7, line 183): It may be useful to pre-specific any subgroups that may be relevant and of interest to explore further. The authors may want to consider conducting meta-regression to evaluate whether the covariates have significant influence on the heterogeneity.

Response: We thank you for this comment. We added the following paragraph:
“Regarding subgroups, we assume it will be relevant to include subgroups regarding the tool used by software to identify targets: STOPP/START criteria subgroup and the Beers criteria. subgroup We will also conduct meta-regression to evaluate whether the covariates have significant influence on heterogeneity.
The studies rated as having a high risk of bias will be included and then analysed in a sub-group analysis. They will be included for the discussion topic.”

7) Reporting bias (Page 7, line 188): The authors may want to consider including funnel plot and statistical tests in the assessment of reporting bias.

Response: We thank you for this suggestion. We added the information that
“In order to determine whether reporting bias is present, we will include funnel plot and statistical tests in the assessment of reporting bias.”

8) Randomized studies (Page 7, line 201): It was not clear why the authors decided to use “generic inverse variance” in the presence of cluster-randomization method.

Response: We thank you for your remark. We have deleted that sentence.

9) Dichotomous data (Page 7, line 205): It may not be necessary to exclude data just because there were zero events. The authors may want to consider using zero-cell correction methods – please refer to the Cochrane Handbook for more details and references.

Response: Thank you. We added this sentence
“When a study reports zero events in both arms we will consider using zero-cell correction methods.”

10) Discussion (Page 8, line 208): The authors may wish to consider mentioning any limitations of this systematic review?

Response: We thank you. We added these limitations:
“One potential limitation to this study will be if we find a limited number of studies with clinical outcomes measured.”

Reviewer#2

1. Keywords; there is a mismatch between keywords given in after the abstract and in the submitting scheme. I would belive that potentially inappropriate medicines could be included.

Response:We thank you for this suggestion. We added the potentially inappropriate medicines and we solved the mismatch.

2. Maybe it is a formatting problem, but some of the words are merged togheter.

Response: We thank you for this remark. We have corrected this formatting problem.

3. Line 98-100 can you please give examples of opportunities and barriers along with references?

Response: We thank you for this comment. We added the following text
Recent studies have identified that interventions such as pharmaceutical care appear beneficial in reducing inappropriate prescribing (9). Although family doctors want to learn more through mobile technologies (10), the doctors´ perspective is that there is insufficient emphasis on geriatric pharmacotherapy training (11)
The references are:
• survey PCISoW. PCI Survey: Family doctors want education on a smartphone2017. Available from: https://www.dropbox.com/s/4vy5o2kdhz7ji8z/WONCA%20survey%20summary%20ACv2.pdf?dl=0.
• Cullinan S, Fleming A, O'Mahony D, Ryan C, O'Sullivan D, Gallagher P, et al. Doctors' perspectives on the barriers to appropriate prescribing in older hospitalized patients: a qualitative study. British journal of clinical pharmacology. 2014;79(5):860-9.
• Patterson SM, Cadogan CA, Kerse N, Cardwell CR, Bradley MC, Ryan C. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev. 2014;10.

4. Line 101-103 does not make sense; please rephrase or elaborate

Response: We thank you for this remark. We changed this phrase to: “It is already proved that computerized decision support systems can reduce physician orders of unnecessary tests (12).”

5. I don't think that we will be able to eliminate inappropriate prescribing; but the purpose of computerised decision support system is to reduce PIMs, and increase omitted drugs.

Response: We thank you for this comment. We changed this statement to “This systematic review aims to determine if computerized decision support is effective in reducing potentially inappropriate medicines”.

6. You state in your aim "in terms of health outcomes"; are there any specific outcomes that you have in mind; or that you (from the litterature) are aware of?

Response: We thank you for your remark. In the “Data Items” we have included this paragraph “The primary outcome is effect of intervention on withdrawal of potentially inappropriate medication (discontinuation rate).
The authors will give priority to the following outcomes, by order of importance: mortality, hospitalization, any reported adverse drug withdrawal effects and quality of life measurement.”

7. In the paragraph concerning data synthesis you state that you will present "the range of clinical decision support"; I don't think this is in accordance to your aim.

Response: Thank you. We have changed this item to “The final report will present the data available of the computer decision support to reduce inappropriate medication in older adults.”

8. PubMed is not a database...but a search engine... Medline is... Have you considered to include ISI web of science?

Response: We thank you for your remark. We changed PubMed to Medline. We will include the ISI Web of science in our search.

9. You state in the discussion section that this review "will help identify the best decision support available, as well as it limitations"; I'm not sure if I agree that by doing this review you will be able to do so; computerised decision systems and how easily they integrate with other softwares would, from my point of view, determine the success of such tools, at least, to a certain extent.

Response: We thank you for this comment. We have changed this phrase to “This systematic review will help identify the success of computerized decision support to reduce inappropriate medication”.

Reviewer#3:

1. The population of interest should be described in more detail: Do the authors plan to include trials conducted with the general older population or with older adults with particular diseases? Also, the authors should explain how potentially inappropriate medications/prescriptions are defined. Furthermore, it is not clear, if the systematic review focuses on the reduction of potentially inappropriate medications (line 63) or on the decrease of potentially inappropriate prescriptions (line 104). Usually, these terms are not used synonymously.

Response: We thank you for this comment.
We added these paragraphs “We will include trials with the general older population and studies with older adults with particular diseases. Potentially inappropriate medications will be defined using the Beers Criteria (14) and STOPP/START Criteria (15).”
We have also changed the phrase potentially inappropriate prescriptions to potentially inappropriate medications.

4. The exclusion/inclusion criteria for the study selection process should be reported in more detail. The search strategy is not thorough enough: For example, the search in the pubmed database only consist of (three) mesh-terms. Consultation with a professional (e.g., a librarian) is recommended. Also, cross-referencing should be performed

Response: We thank you for your comment. We have changed our search. Please see response to the 3rd comment of the first reviewer.
We also added the following paragraph: “Reference lists will be checked in order to identify additional relevant studies to be included in the systematic review.”

Comment: In lines 150,151 the authors declare the use of data sheets. However, they do not describe the development or the contents of these sheets any further.

Response: Thank you. We added this paragraph “These sheets will also include the study reference, intervention type, study design, country, setting, follow-up, number of participants, age, effect pf intervention on reducing potential inappropriate medications, clinical outcomes.”

Comment: The authors plan to perform a risk of bias assessment. However, they do not state how they plan to use this information in the data synthesis. The results could be used to perform sensitivity analyses by excluding those studies with high risk of bias.

Response: We thank you for your remark. We added this information in the “Data Synthesis” section: “The studies rated as high risk of bias will be included and will be analysed in a sub-group analyses.”

6. The authors should define the outcomes more detailed. It is not clear, if the authors plan to examine all possible clinical outcomes or only certain ones. Also, the authors should define the primary endpoint (reduction of potentially inappropriate medication?) and the secondary endpoint.

Response: Thank you. We have defined the outcomes with more detail: “3) outcomes:
The primary outcome is effect of intervention on withdrawal of potentially inappropriate medication (discontinuation rate). The authors will give priority to the following clinical outcomes: hospitalization, mortality, any reported adverse drug withdrawal effects and quality of life measurement.”

7. The authors plan to decide on the random or fixed effects model based on the statistically calculated heterogeneity (see lines 171, 172, 176, 177). This should not be done. According to the Cochrane Handbook for Systematic Reviews of Interventions, the decision should be made in advance to the analyses, based on clinical assumption or the study situation.

Response: We thank you for your remark. We have changed this paragraph also following the comment of the reviwer #1: “We changed the model to random model.

Furthermore, the authors report the statistical methods to be used in a rather general manner (compare lines 174,175).
We completed the statistical methods information:
“The final report will present the available data of the computer decision to support or reduce inappropriate medications in older adults.
Each outcome will be combined and calculated using the statistical software RevMan 5.1 (17), according to statistical guidelines referenced in the current version of the Cochrane Handbook for Systematic Reviews of Interventions(18). If heterogeneity is substantial, we will not perform a meta-analysis; thus, a narrative, qualitative summary will be done instead.
Subgroups will be presented according to the setting, intervention, and medication. The final paper will be prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (19, 20).
Subgroup analyses will be used to explore possible sources of heterogeneity, based on the following: medications and type of software.
Regarding subgroups, we assume it will be relevant to include subgroups regarding the tool used by software to identify targets: STOPP/START criteria subgroup; Medication Appropriateness subgroup and the Beers criteria. subgroup We will also conduct meta-regression to evaluate whether the covariates have significant influence on heterogeneity.
The studies rated as having a high risk of bias will be included and then analysed in a sub-group analysis. They will be included for the discussion topic.
A systematic narrative synthesis will be provided in the text and tables to summarise and explain the characteristics and findings of the studies; it will explore the relationship within and between studies, in line with guidance from the Centre for Reviews and Dissemination.
In order to determine whether reporting bias is present, we will include funnel plot and statistical tests in the assessment. We will determine whether the protocol of the RCT was published before recruitment of patients was initiated.
Data from RCTs will not be combined with data from other study designs. We will evaluate whether selective reporting of outcomes is obvious. The quality of evidence for all outcomes will be judged with the Grading of Recommendations Assessment, and the Development and Evaluation working group methodology (21).We further separated comparative studies with and without concurrent control groups. Forest plots will be produced when three or more studies are included in a meta-analysis. Data in tables will be presented by therapeutic class, based on the Anatomical Therapeutic Classification (ATC) codes.
Randomized studies:
If heterogeneity is detected, we will select the random effects model.
Dichotomous data:
Effect sizes and 95% confidence intervals (CIs)were expressed as odds ratios (OR). When a study reports zero events in both arms, we will consider using zero-cell correction methods.
.”

8. The authors make statements without providing any references for proof (e.g., lines 89, 94, 100).

Response: We thank you for your comment. We added references to those statements:
• Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. Ageing research reviews. 2011;10(4):430-9.
• Prazeres F, Santiago L. Prevalence of multimorbidity in the adult population attending primary care in Portugal: a cross-sectional study. BMJ open. 2015;5(9):e009287.
• Hanlon JT, Schmader KE, Ruby CM, Weinberger M. Suboptimal prescribing in older inpatients and outpatients. Journal of the American Geriatrics Society. 2001;49(2):200-9.
• Weng MC, Tsai CF, Sheu KL, Lee YT, Lee HC, Tzeng SL, et al. The impact of number of drugs prescribed on the risk of potentially inappropriate medication among outpatient older adults with chronic diseases. QJM : monthly journal of the Association of Physicians. 2013;106(11):1009-15.
• Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. Jama. 2007;297(11):1233-40.

Furthermore, the authors cite at least one incorrect reference (see line 97). The correct reference is the following:
Reeve E, Gnjidic D, Long J, Hilmer S (2015) A systematic review of the emerging definition of "deprescribing" with network analysis: implications for future research and clinical practice. Br J Clin Pharmacol. 2015; 80(6):1254–1268)
We thank you for your comment. We have corrected that citation.

13. The PRISMA checklist is incomplete: The authors did not choose Yes or No for the items 4, 5c, 6, 7, and 9 to 17.
Furthermore, some of the line numbers are obviously incorrect (e.g., #12, #15c, #16).

Response: We thank you for your comment. We have completed the PRISMA checklist and corrected the line numbers.

15. The text contains a lot of typing errors and spelling mistakes. Some sentences are unintelligible. Also, there are incoherent sentences, especially in the abstract and introduction, and an inconsistent choice of wording (e.g. pubmed
- MEDLINE). Revision by a native speaker is strongly recommended.

Response: We thank you for your remark. We edited the manuscript and the reference to Pubmed has been replace by Medline.
The manuscript had already been edited by a professional native English-speaking academic editing service. After the changes we have done during this review we have submitted it once more to Academic English editing service.

VERSION 2 – REVIEW

REVIEWER	Dr Tau Ming LIEW 1) Institute of Mental Health, Singapore 2) Saw Swee Hock School of Public Health, National University of Singapore
REVIEW RETURNED	15-Oct-2017

GENERAL COMMENTS	Thank you for considering my previous comments and making the necessary changes. The current manuscript is much more ready for publication. A few minor comments: 1) Page 4, line 107: "Although family doctors want to learn more through mobile technologies (10), the doctors´ perspective is that there is insufficient emphasis on geriatric pharmacotherapy training (11) ". This sentence appeared disjointed from the previous sentence and the exact message that the author is intending to convey is not so clear. 2) Page 6, line 153. For the search term, it will also be relevant to include the keywords of "inappropriate prescribing" and "deprescribing" (apart from the mesh terms). 3) Page 8, line 236. "If heterogeneity is detected , we will select the random effects model." Heterogeneity should have minimal influence on the choice of random effects model. Please see the comments by previous reviewer 3 on this (with reference to Cochrane handbook). 4) Page 9, line 253. "One potential limitation of this study will be if we find a limited number of studies with clinical outcomes measured. " This sentence is not so clear. Do you mean that if limited number of studies are found, meta-analysis cannot be conducted? 5) Are there other limitations that you will like to mention? Eg. the last point mentioned by previous reviewer 2. Thank you and all the best! Looking forward to seeing your meta-analysis.

REVIEWER	Kjell H. Halvorsen Department of Pharmacy, The Arctic university of Norway
REVIEW RETURNED	31-Oct-2017

GENERAL COMMENTS	You need to rewrite the search strategy for Web of Science. It is not possible to just copy and paste the one used for searching Medline. There is a set of Booleans (e.g AND, OR, NOT, SAME, NEAR) and field tags that you need to consider when searching web of science. Otherwise I think the authors have responded adequately to my former concerns.

REVIEWER	Ben Schöttker German Cancer Research Center Germany
REVIEW RETURNED	26-Oct-2017

GENERAL COMMENTS	1. According to the authors, the main novelty of their work will be a meta-analysis (compare lines 112,113). However, in lines 199 to 200 they also write that they will not perform a meta-analysis if heterogeneity between the studies is too high. It might be advisable not only to focus on the meta-analysis as a unique feature, but also on other aspects of the work. Otherwise, the work might appear redundant. 2. It may be helpful if the statistical methods are reported in more detail. For example, the authors write: “In order to determine whether reporting bias is present, we will include funnel plot and statistical tests in the assessment” (lines 215-216). However, they do not explain which statistical tests they plan to use.

	3. I recommend including the definitions of "polypharmacy", "inappropriate prescribing" and "potentially inappropriate medicines" the first time these terms are mentioned in the text (page 4, lines 94, 105 and 110). 4. The authors still plan on using the random effects model based on the presence of heterogeneity (compare page 8, line 226: “If heterogeneity is detected, we will select the random effects model.”). As mentioned before, the decision to use the random or the fixed effects model should be made in advance depending on the study situation. 5. Sections of the paper appear unclear or confusing. For example, the argumentation about the importance and novelty of the work seems to be incomplete (compare page 4, lines 108 to 113). Also, the specification of the subgroups are not described coherently and are therefore quite difficult to understand. 6. Concerning the writing style and the language: There are still some typing errors (e.g., line 65: “decision”), and grammatical errors (e.g., line 58 “it is been demonstrated”). Also, the quotation marks in lines 67/68 seem unnecessary? A personal recommendation: The introduction still seems incoherent to me and appears more like a list of independent sentences. I think it would enhance the readability of the text if the authors used logical links between the sentences.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Thank you for considering my previous comments and making the necessary changes. The current manuscript is much more ready for publication. A few minor comments:
1) Page 4, line 107: "Although family doctors want to learn more through mobile technologies (10), the doctors´ perspective is that there is insufficient emphasis on geriatric pharmacotherapy training (11) ". This sentence appeared disjointed from the previous sentence and the exact message that the author is intending to convey is not so clear.

Response: We thank you for your comments that helped us greatly to improve our article.
We have made several changes in the introduction section. This sentence was modified as following: Inappropriate medication prescription, meaning “the practice of administering medications in a manner that poses more risk than benefit, particularly where safer alternatives exist”(5, 11) , can be reduced by several interventions (12). However, they are not widely known and therefore used. In one hand, general practitioners report interest in learning and using more mobile technologies to assist in clinical care (13); on the other they refer an insufficient emphasis on geriatric pharmacotherapy training (14).

2) Page 6, line 153. For the search term, it will also be relevant to include the keywords of "inappropriate prescribing" and "deprescribing" (apart from the mesh terms).

Response: Thank you for your suggestion. We have changed our query for MEDLINE, to “(Medical Informatics Applications [MeSH Terms] OR (medical AND informatics AND applications)) AND ((Deprescriptions [Mesh Terms] OR deprescription OR deprescribing OR Inappropriate Prescribing [Mesh Terms] OR (inappropriate AND prescribing*) OR (inappropriate AND prescription*) OR (over* AND prescribing*)) OR medication errors [MeSH Terms] OR (error* AND medication) OR (drug AND use AND error*) AND (decision support systems, clinical [MeSH Terms] OR “clinical decision support

systems” OR (clinical AND decision AND support*) OR decision making, computer-assisted [MeSH Terms] OR (computer AND assisted AND decision AND making) OR (medical AND computer AND assisted AND decision AND making) OR medical order entry systems [MeSH Terms] OR (medical AND order entry systems) OR (medications AND alert AND systems) OR “computorized physician order entry systems” OR “computorized provider order entry systems” OR “computorized physician order entry” OR “computorized provider order entry”)”

3) Page 8, line 236. "If heterogeneity is detected, we will select the random effects model." Heterogeneity should have minimal influence on the choice of random effects model. Please see the comments by previous reviewer 3 on this (with reference to Cochrane handbook).

Response: We have acknowledge your comment and changed the above sentence to the following one: “If we are able to include a group of studies that are sufficiently comparable and reliable we will conduct a meta-analysis. We consider that we should use a random effect model taking in consideration the previous systematic reviews’ results. We expect to encounter a sufficient number of studies, reporting a sufficient number of events, but that are not completely comparable (concerning the intervention, context and population).
If heterogeneity is severe (I2 superior to 40-50%) and studies’ results are strongly biased, we will not perform a meta-analysis; thus, a narrative, qualitative summary will be done instead.”

4) Page 9, line 253. "One potential limitation of this study will be if we find a limited number of studies with clinical outcomes measured." This sentence is not so clear. Do you mean that if limited number of studies are found, meta-analysis cannot be conducted?

Response: We rephrased the referred sentence to make it clearer: “One potential limitation of this study will be if we find a limited number of studies with considerable differences regarding their characteristics and methodology. This may impair our conclusions and impede meta-analysis.”

5) Are there other limitations that you will like to mention? Eg. the last point mentioned by previous reviewer 2.

Response: We have added the following information: “In addition, depending on the data available and obtained results we may not be able to define which is the best decision support available.”

Thank you and all the best! Looking forward to seeing your meta-analysis.
Thank you for given us the opportunity to improve our protocol.

Reviewer: 2
You need to rewrite the search strategy for Web of Science. It is not possible to just copy and paste the one used for searching Medline. There is a set of Booleans (e.g AND, OR, NOT, SAME, NEAR) and field tags that you need to consider when searching web of science. Otherwise I think the authors have responded adequately to my former concerns.
Thank you for your comment. We have modified the search strategy on this database to: “For Web of Science the query will be “TS=(“Medical Informatics Applications” OR (medical AND informatics AND applications)) AND TS=((Deprescriptions OR deprescription OR deprescribing OR “Inappropriate Prescribing” OR (inappropriate AND prescribing*) OR (inappropriate AND prescription*) OR (over* AND prescribing*)) OR “medication errors”OR (error* AND medication) OR (drug AND use AND error*) AND TS=(“clinical decision support systems” OR (clinical AND decision AND support*) OR decision making, computer-assisted [MeSH Terms] OR (computer AND assisted AND decision AND making) OR (medical AND computer AND assisted AND decision AND making) OR “medical order entry systems” OR (medical AND order entry systems) OR (medications AND alert AND systems) OR

“computorized physician order entry systems” OR “computorized provider order entry systems” OR “computorized physician order entry” OR “computorized provider order entry”).”

Reviewer: 3
1. According to the authors, the main novelty of their work will be a meta-analysis (compare lines 112,113). However, in lines 199 to 200 they also write that they will not perform a meta-analysis if heterogeneity between the studies is too high. It might be advisable not only to focus on the meta-analysis as a unique feature, but also on other aspects of the work. Otherwise, the work might appear redundant.

Response: We have changed several sentences throughout the protocol in order to remove the emphasis of the meta-analysis but highlighting the importance of conducting a comprehensive systematic review on the subject.

2. It may be helpful if the statistical methods are reported in more detail. For example, the authors write: “In order to determine whether reporting bias is present, we will include funnel plot and statistical tests in the assessment” (lines 215-216). However, they do not explain which statistical tests they plan to use.

Response: We have included the following information In order to determine whether publication bias is present, we will include funnel plot and statistical tests in the assessment, namely Begg’s and Egger’s test.”

3. I recommend including the definitions of "polypharmacy", "inappropriate prescribing" and "potentially inappropriate medicines" the first time these terms are mentioned in the text (page 4, lines 94, 105 and 110).

Response: Thank you for your remark. The last concept is considered by us as a synonym of inappropriate prescribing. As this could be considered as not clear we have standardized our manuscript and tried to use only the “inappropriate medication prescription” expression.
We have added the suggested definitions of "polypharmacy" and "inappropriate prescribing” in the following sentences: “Polypharmacy, defined as “the use of multiple drugs administered to the same patient, most commonly seen in elderly patients”(5, 6), although frequent has a negative impact on senior health (7, 8). (…)Inappropriate medication prescription, meaning “the practice of administering medications in a manner that poses more risk than benefit, particularly where safer alternatives exist” (5, 11), can be reduced by several interventions (12).”

4. The authors still plan on using the random effects model based on the presence of heterogeneity (compare page 8, line 226: “If heterogeneity is detected, we will select the random effects model.”). As mentioned before, the decision to use the random or the fixed effects model should be made in advance depending on the study situation.

Response: We are very sorry for not making the suggested modification in the last revision moment. We hope to fulfil your requests by including the following sentence: “If we are able to include a group of studies that are sufficiently comparable and reliable we will conduct a meta-analysis. We consider that we should use a random effect model taking in consideration the previous systematic reviews’ results. We expect to encounter a sufficient number of studies, reporting a sufficient number of events, but that are not completely comparable (concerning the intervention, context and population). If heterogeneity is severe (I2 superior to 40-50%) and studies’ results are strongly biased, we will not perform a meta-analysis; thus, a narrative, qualitative summary will be done instead.”

5. Sections of the paper appear unclear or confusing. For example, the argumentation about the importance and novelty of the work seems to be incomplete (compare page 4, lines 108 to 113). Also, the specification of the subgroups are not described coherently and are therefore quite difficult to understand.

Response: Thank you very much for your comment. We have corrected the protocol in what concerns such incongruences.

6. Concerning the writing style and the language: There are still some typing errors (e.g., line 65: “decision”), and grammatical errors (e.g., line 58 “it is been demonstrated”). Also, the quotation marks in lines 67/68 seem unnecessary?

Response: We have reviewed the entire article again and made substantial changes.

Comment: A personal recommendation: The introduction still seems incoherent to me and appears more like a list of independent sentences. I think it would enhance the readability of the text if the authors used logical links between the sentences.
Response: Thank you for your comment. We have edited the introduction in order to improve its readability.