PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	What are the important design features of personal health records to improve medication adherence for patients with long term conditions? A systematic literature review.
AUTHORS	Andrikopoulou, Elisavet; Scott, Philip; Herrera, Helena; Good, Alice

VERSION 1 – REVIEW

REVIEWER	Mary Ann Forciea MD University of Pennsylvania Health System Philadelphia PA USA
REVIEW RETURNED	14-Jan-2019

GENERAL COMMENTS	I do not see the search terms listed in the 'Literature Search' section of the manuscript (page 5). While the questions asked in the manuscript are important, the paucity of good quality studies is frustrating. I do think the author's clearly and adequately describe their inability to make strong conclusions from the data.

REVIEWER	Debi Bhattacharya University of East Anglia, UK
REVIEW RETURNED	19-Feb-2019

GENERAL COMMENTS	A novel research topic with potential for utility in the clinical setting. Abstract Objectives: This systematic literature review aims to identify important design features of the electronic personal health record (PHR) that may improve medication adherence in the adult population with long-term conditions and whether implementation factors or demographics interact with the PHR impact This is a very long sentence with multiple clauses. I recommend splitting: This systematic literature review aims to identify important design features of the electronic personal health record (PHR) that may improve medication adherence in the adult population with long-term conditions. The latter part of this sentence is less clear – what is meant by impact? From reading the objectives which are written in the future tense, I had assumed that this is a protocol paper, however, it is the

	findings paper thus the tense needs to be changed to past tense i.e. “this study aimed to…” The abstract results characterise the quality of included and excluded studies and participant characteristics e.g. participants were largely represented by the medical conditions diabetes and HIV. However, the study objective was to report design features and this is what is absent in the abstract. Please pair back the detail regarding adherence measurement and participant characteristics to include the information core to the study objectives i.e. the 12 design features. Introduction I appreciate that the target journal is BMJ open, however, the introduction feels overly UK centric, particularly the opening paragraph. Lines 22-30 ‘Some of the indicated benefits of PHRs are the ability of PHR to improve patient outcomes, decrease care cost, allow patients the ability to self-manage their health, increase access to care especially in remote areas, empower patients and improve medication adherence.[6,7] Medication adherence is a well-known challenge in healthcare,[8,9] but there is limited evidence whether PHRs actually improve medication adherence in chronically ill adults and no evidence synthesis as to which PHR design features are the most effective.’ Given that the manuscript is about the effects of PHR on adherence, I think that the existing evidence needs greater consideration i.e. a little more discussion about references 6 and 7. Page 3 Line 33 You introduce the ABC taxonomy but provide no indication of how this relates to the present SR. Page 4 study eligibility The review included both primary studies and reviews – please provide greater detail regarding how these two very different types data were handled. This is currently a significant limitation – why are the primary studies from the reviews not included – are they included and therefore duplicated? Literature search All screening (titles, abstracts and full texts) was undertaken by one author with referral to a second author only if the first author was uncertain. There is therefore at no point, independent screening of the included / excluded studies. This is a significant limitation not recognised in the limitations section. Data extraction and analysis Page 5 Lines 18 and 19 Please provide more detail regarding what is meant by all data were extracted by one author and validated by a second author. What was the validation process? Independently extracted by a second author? If that is the case, I’d like to see some agreement data reported. If not, this again introduces high risk of error.

	Risk of bias – please reference the Cochrane handbook (an international audience will be less familiar with Cochrane) and in the abstract, the authors refer to 'Cochrane RevMan tool', RevMan is the name of software that includes the Cochrane tool so please refer to the Cochranre risk of bias tool rather than RevMan tool. Please review the manuscript for grammatical errors – there are quire a few 'of's missing. Page 5 lines 6 and 7 'Most studies had included participants, which have [at is missing here] least one long term condition (n=9), diabetes (n= 5) and HIV (n=3). Most studies were published in 2014 (n=6…' Page 36 – quality assessment The inter-rater reliability between EA and PS was calculated to k=0.88, which indicates that the reliability of the quality assessment is likely to be high There is no reference to inter-rater reliability being calculated in the methods – K is reported – what about p? Overall, the main issues are with the conduct/reporting of the methods. The inclusion of systematic reviews and then not reporting the intervention details is problematic - table 2 simply reports 'more than one' for SRs so that for all of these studies, the review has no indication of what the intervention is. Given that the study aim was do describe design features supportive of adherence, this study needs to only include the primary literature and describe the design features of PHRs. The authors therefore need to return to the SRs and identify the included primary studies. It would also be useful to know the date when the searches were run to establish how contemporaneous the findings are.

REVIEWER	Marie-Pierre Gagnon Université Laval, Canada
REVIEW RETURNED	02-Mar-2019

GENERAL COMMENTS	Thank you for the opportunity to review this paper that explores the link between design features of electronic personal health records (PHR) and medication adherence, based on a systematic review of the literature. Although the topic is important for the field of eHealth, there are some points that need more clarification. 1. The rationale for focusing on "design features" is not clear. In the Introduction, the benefits of PHRs are presented, as well as the issue of medication adherence. But a section discussing the importance of design for improving self-management is missing. So, before the sentence "This is the first systematic literature review that aims to identify important design features of the PHR that may improve medication adherence in the adult population with long-term conditions", it is important to know why design features are important in the way PHR improves medication adherence. The features that are presented in Table 3 should be introduced in the Introduction, so the reader knows which particular features were considered. 2. It is also difficult to understand the rationale of the secondary objectives. The objectives will probably be more relevant if the rationale for the review question is better explained, for instance

	explaining why polymedication can be an issue, and which particular chronic diseases should benefit from managing medication through PHRs. 3. In the Methods section, please indicate the precise date of searches instead of “the last fifteen years" (e.g. January 1st, 2004-Dec. 31st, 2017). 4. The selection was made by one author only (except in case of uncertainty) while the standards in systematic reviews are that 2 people do the selection independently, so this should be reported as a weakness. 5. In the Results section, the number of included studies is said to be 23 (p. 5). However, in the section Characteristics of included studies, it becomes very confusing. First, it is said that there are 7 studies from the USA, 7 from multiple countries, and 2 from Switzerland. These add up to 16 and not 23… And the same confusion is present for the other characteristics. The numbers should always be reported based on the total sample of studies that is 23. 6. The other confusing point is the fact that low quality studies were excluded from the analyses, so does it mean that they are not reported at all in this paper? Then, it should be clearly stated in the Methods that low study quality was an exclusion criteria. 7. The inclusion of systematic reviews is questionable because they do not provide the same level of information as primary studies. What was the added value of including systematic reviews? If the search strategy was efficient, then all the relevant studies from the time period of interest should have been found. Consulting systematic reviews to identify other potentially eligible primary studies would be acceptable, but including them at the same level as primary studies is not recommended. Previous systematic reviews have their proper inclusion and exclusion criteria that do not necessarily match yours. For instance, a primary study that is older than 15 years might be included in a systematic review. Also, a systematic review may contain primary studies that have already been included, thus giving more weight to the results of these studies. Was this checked? 8. A reference is needed for the sentence “It could also mean that some of these results are less accurate, due to lower number of participants, since there is uncertainty towards the validity of the results derived from RCTs with less than 100 participants.” (p. 13). 9. The Discussion section does not provide much comparison with other studies on the main research question that is ‘Are design features of PHR influencing medication adherence?’ To do so, findings from previous studies supporting that certain design features of PHR influence medication adherence should be discussed. 10. There is a lot of emphasis on the ‘other bias’ category, but it is not clear what are these other bias (there a list in the Methods section, but it is not referred to in the Discussion). 11. The GRADE approach consists of 5 domains (risk of bias, inconsistency, indirectness, imprecision and publication bias. However, only the implications related to of bias are discussed. What about the other domains? 12. There should be a separate conclusion presenting the main findings and implications for future research.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
I do not see the search terms listed in the 'Literature Search' section of the manuscript (page 5).
Very important comment, which prompt us to add a new paragraph in methods>literature search to include the search terms and a new supplementary file with the full search strategy.

Reviewer 2
Abstract Objectives: This systematic literature review aims to identify important design features of the electronic personal health record (PHR) that may improve medication adherence in the adult population with long-term conditions and whether implementation factors or demographics interact with the PHR impact. This is a very long sentence with multiple clauses. I recommend splitting: This systematic literature review aims to identify important design features of the electronic personal health record (PHR) that may improve medication adherence in the adult population with long-term conditions. The latter part of this sentence is less clear – what is meant by impact?
This was a great suggestion and we totally agree. The unclear part of the sentence about impact is now removed.

From reading the objectives which are written in the future tense, I had assumed that this is a protocol paper, however, it is the findings paper thus the tense needs to be changed to past tense i.e. “this study aimed to…”
Thank you. That was an honest mistake and is now corrected. The objectives are in past tense.

The abstract results characterise the quality of included and excluded studies and participant characteristics e.g. participants were largely represented by the medical conditions diabetes and HIV. However, the study objective was to report design features and this is what is absent in the abstract. Please pair back the detail regarding adherence measurement and participant characteristics to include the information core to the study objectives i.e. the 12 design features.
This was a great suggestion. The identified design features are now included, keeping as much information as possible.

Introduction. I appreciate that the target journal is BMJ open, however, the introduction feels overly UK centric, particularly the opening paragraph.
Fair point. We included some global examples and details in introduction paragraph 1

Lines 22-30. ‘Some of the indicated benefits of PHRs are the ability of PHR to improve patient outcomes, decrease care cost, allow patients the ability to self-manage their health, increase access to care especially in remote areas, empower patients and improve medication adherence.[6,7] Medication adherence is a well-known challenge in healthcare,[8,9] but there is limited evidence whether PHRs actually improve medication adherence in chronically ill adults and no evidence synthesis as to which PHR design features are the most effective.’ Given that the manuscript is about the effects of PHR on adherence, I think that the existing evidence needs greater consideration i.e. a little more discussion about references 6 and 7.
Your comment made us realise that we indeed need to be more explicit. Medication adherence and its link to PHRs are explained in more depth now in the introduction and it will provide a better understanding on the effects of PHR on adherence.
Page 3 Line 33 You introduce the ABC taxonomy but provide no indication of how this relates to the present SR.
In the light of this comment we have changed our minds and decided to exclude this taxonomy. We initially planned to use it, but we have decided against it when we reviewed the relevant literature.

Page 4 study eligibility The review included both primary studies and reviews – please provide greater detail regarding how these two very different types data were handled. This is currently a significant limitation – why are the primary studies from the reviews not included – are they included and therefore duplicated?
This was a great suggestion and we totally agree regarding the added limitations and potential duplication of information. In the light of this comment we have decided to exclude the systematic reviews and to continue our review with only primary studies.
Changes:
• Abstract
• Table 1 study design/type
• Figure 1 PRISMA diagram
• Results>literature search results
• Results>characteristics paragraph 1
• Table 2 included primary studies
• Table 3 PHR design features
• Results>primary objectives bullet points at the end of the section.
• Results>secondary objectives>diabetes
• Results>secondary objectives>association between participants demographics… paragraph 1
• Results>quality assessment
• Discussion paragraph 1,2 and 3

Literature search All screening (titles, abstracts and full texts) was undertaken by one author with referral to a second author only if the first author was uncertain. There is therefore at no point, independent screening of the included / excluded studies. This is a significant limitation not recognised in the limitations section.
This is an important comment. It is now reported according to suggestions in discussion last paragraph.

Page 5 Lines 18 and 19Please provide more detail regarding what is meant by all data were extracted by one author and validated by a second author. What was the validation process? Independently extracted by a second author? If that is the case, I'd like to see some agreement data reported. If not, this again introduces high risk of error.
Thank you for your comment. We made a clarification change in methods> data extraction and analysis section and see also the first line of quality assessment. This limitation is now reported in discussion section, last paragraph.

Risk of bias – please reference the Cochrane handbook (an international audience will be less familiar with Cochrane) and in the abstract, the authors refer to 'Cochrane RevMan tool', RevMan is the name of software that includes the Cochrane tool so please refer to the Cochranre risk of bias tool rather than RevMan tool.
Thank you this was an important comment and is now corrected according to suggestions.

Please review the manuscript for grammatical errors – there are quire a few 'of's missing.
This comment prompted us to ask some colleagues to proofread the manuscript further. We hope that we have rectified any issues.

Page 5 lines 6 and 7 'Most studies had included participants, which have [at is missing here] least one long term condition (n=9), diabetes (n= 5) and HIV (n=3). Most studies were published in 2014 (n=6…'
Thank you. That was a typo mistake and is now corrected.

Page 36 – quality assessment The inter-rater reliability between EA and PS was calculated to k=0.88, which indicates that the reliability of the quality assessment is likely to be high. There is no reference to inter-rater reliability being calculated in the methods – K is reported – what about p?
Thank you for your comment. We have added a reference regarding Cohen's Kappa calculation in methods > quality assessment.
According to health-informatics literature (Friedman & Wyatt, 2006; McHugh, 2012), Cohen's Kappa (k) is the index that compares the agreement between authors. According to the sources, there is no specific need to calculate the p value as k indicates sufficiently the inter-rater reliability.
Friedman, C. P., & Wyatt, J. (2006). Evaluation methods in biomedical informatics.
McHugh, M. L. (2012). Interrater reliability: the kappa statistic. Biochemia Medica, 22(3), 276–282. PMCID: PMC3900052

Overall, the main issues are with the conduct/reporting of the methods. The inclusion of systematic reviews and then not reporting the intervention details is problematic - table 2 simply reports 'more than one' for SRs so that for all of these studies, the review has no indication of what the intervention is. Given that the study aim was do describe design features supportive of adherence, this study needs to only include the primary literature and describe the design features of PHRs. The authors therefore need to return to the SRs and identify the included primary studies. It would also be useful to know the date when the searches were run to establish how contemporaneous the findings are.
Thank you for your comment. In the light of this comment, and the overall comments made by all the reviewers, we have decided to exclude the systematic reviews and report only on primary studies. The mentioned table and the entire manuscript have been altered accordingly.
Changes:
• Abstract
• Table 1 study design/type
• Figure 1 PRISMA diagram
• Results>literature search results
• Results>characteristics paragraph 1
• Table 2 included primary studies
• Table 3 PHR design features
• Results>primary objectives bullet points at the end of the section.
• Results>secondary objectives>diabetes
• Results>secondary objectives>association between participants demographics… paragraph 1
• Results>quality assessment
• Discussion paragraph 1,2 and 3

Reviewer 3
The rationale for focusing on "design features" is not clear. In the Introduction, the benefits of PHRs are presented, as well as the issue of medication adherence. But a section discussing the importance of design for improving self-management is missing. So, before the sentence "This is the first systematic literature review that aims to identify important design features of the PHR that may improve medication adherence in the adult population with long-term conditions", it is important to know why design features are important in the way PHR improves medication adherence. The features that are presented in Table 3 should be introduced in the Introduction, so the reader knows which particular features were considered.
We thank you for this comment. We have now modified the introduction to include clear references of polypharmacy, long-term conditions and HCI notions and their relationships (paragraphs 4, 5, 6 of introduction).

It is also difficult to understand the rationale of the secondary objectives. The objectives will probably be more relevant if the rationale for the review question is better explained, for instance explaining

why polymedication can be an issue, and which particular chronic diseases should benefit from managing medication through PHRs.
See comment above.

In the Methods section, please indicate the precise date of searches instead of “the last fifteen years" (e.g. January 1st, 2004-Dec. 31st, 2017).
This is an important comment. It is now corrected according to suggestions in methods > literature search section.

The selection was made by one author only (except in case of uncertainty) while the standards in systematic reviews are that 2 people do the selection independently, so this should be reported as a weakness.
This is a very important comment. It is now reported according to suggestions in the last paragraph of discussion.

In the Results section, the number of included studies is said to be 23 (p. 5). However, in the section Characteristics of included studies, it becomes very confusing. First, it is said that there are 7 studies from the USA, 7 from multiple countries, and 2 from Switzerland. These add up to 16 and not 23… And the same confusion is present for the other characteristics. The numbers should always be reported based on the total sample of studies that is 23.
We thank you for this comment. We have now modified the entire document to always report on the entire number of included studies.
Changes:
• Abstract
• Table 1 study design/type
• Figure 1 PRISMA diagram
• Results>literature search results
• Results>characteristics paragraph 1
• Table 2 included primary studies
• Table 3 PHR design features
• Results>primary objectives bullet points at the end of the section.
• Results>secondary objectives>diabetes
• Results>secondary objectives>association between participants demographics… paragraph 1
• Results>quality assessment
• Discussion paragraph 1,2 and 3

The other confusing point is the fact that low quality studies were excluded from the analyses, so does it mean that they are not reported at all in this paper? Then, it should be clearly stated in the Methods that low study quality was an exclusion criteria.
This is a very important comment. It is now clearly reported at the methods section. See: Table 1 Summary of the PICOS elements included and excluded in the systematic review > Quality of the studies

The inclusion of systematic reviews is questionable because they do not provide the same level of information as primary studies. What was the added value of including systematic reviews? If the search strategy was efficient, then all the relevant studies from the time period of interest should have been found. Consulting systematic reviews to identify other potentially eligible primary studies would be acceptable, but including them at the same level as primary studies is not recommended. Previous systematic reviews have their proper inclusion and exclusion criteria that do not necessarily match yours. For instance, a primary study that is older than 15 years might be included in a systematic review. Also, a systematic review may contain primary studies that have already been included, thus giving more weight to the results of these studies. Was this checked?

This was a great suggestion and we totally agree regarding the added limitations and problems. In the light of this comment and also the other reviewer's similar opinion, we have decided to exclude the systematic reviews and to continue our review with reporting only primary studies. Relevant changes have been made throughout the document to depict this decision.
Changes:
• Table 1 study design/type
• Figure 1 PRISMA diagram
• Results>literature search results
• Results>characteristics paragraph 1
• Table 2 included primary studies
• Table 3 PHR design features
• Results>primary objectives bullet points at the end of the section.
• Results>secondary objectives>diabetes
• Results>secondary objectives>association between participants demographics… paragraph 1
• Results>quality assessment
• Discussion paragraph 1,2 and 3

A reference is needed for the sentence "It could also mean that some of these results are less accurate, due to lower number of participants, since there is uncertainty towards the validity of the results derived from RCTs with less than 100 participants." (p. 13).
Thank you for this comment. The sentence is now referenced.

The Discussion section does not provide much comparison with other studies on the main research question that is 'Are design features of PHR influencing medication adherence?' To do so, findings from previous studies supporting that certain design features of PHR influence medication adherence should be discussed.
Thank you for your comment however, a conclusion of our review is that there is no other literature on this specific topic. Therefore, we can only cite general literature about medication adherence and PHR usage, but nothing about the interaction of these two constructs.

There is a lot of emphasis on the 'other bias' category, but it is not clear what are these other bias (there a list in the Methods section, but it is not referred to in the Discussion).
To avoid the appearance of over-emphasising the "other bias" category, we have removed the breakdown of its characteristics from the section methods > quality assessment. See also the next response.

The GRADE approach consists of 5 domains (risk of bias, inconsistency, indirectness, imprecision and publication bias. However, only the implications related to of bias are discussed. What about the other domains?
Thank you for your comment. The breakdown of the GRADE approach and all the necessary details can be found in the additional file.

There should be a separate conclusion presenting the main findings and implications for future research.
This was avoided based on the journal's author instructions.

VERSION 2 – REVIEW

REVIEWER	Marie-Pierre gagnon Université Laval Canada

REVIEW RETURNED	04-Jul-2019

GENERAL COMMENTS	Thank you for your careful consideration of my previous comments. I am happy with the corrections.