PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Does case management for patients with heart failure based in the community reduce unplanned hospital admissions? A systematic review and meta-analysis
AUTHORS	Huntley, Alyson; Johnson, Rachel; King, Anna; Morris, Richard; Purdy, Sarah

VERSION 1 - REVIEW

REVIEWER	Prof Rod Taylor Institute of Health Research University of Exeter Medical School England
REVIEW RETURNED	23-Jan-2016

GENERAL COMMENTS	This paper a systematic review and meta-analysis to assess the clinical effectiveness and cost- effectiveness of case management for patients with heart failure. The manuscript is generally well presented and well conducted. However, there are some major issues that need resolved: - It is not clear why the authors have chosen to include non-RCT evidence (and the risk of confounding and selection bias) in their effectiveness review. A clear rationale needs for the inclusion of non-RCT needs to be provided. - Relatedly, there are two methodological problems with the current study as presented that need to be resolved. First, the Cochrane risk of bias tool is designed specifically for RCTs. The assessment of risk of bias/study quality of non-RCT should be assessed with an appropriate tool. Second, it is not appropriate to combine evidence from RCT and non-RCT evidence. At the very least, the authors should stratify their pooling by study type and examine the variation in effect size by study type. - The consideration of cost-effectiveness evidence is rather superficial in this review. Was a co-author a health economist or formally trained in economic evaluation methods? At the very least, the review should separate out the costs of the intervention, the costs of the downstream healthcare utilisation and (where reported) the incremental cost effectiveness (using methods such as cost per life year gained or QALY). More minor issues for consideration - Abstract: clarify inclusion of both RCT and non-RCT evidence; give the total number of HF patients included in the included trials by community and hospital based CM trials (also in results); as above, be more specific about “cost data”. Suggest reword conclusions to read “There were limited evidence for community-initiated CM reducing hospital admission” - Introduction and discussion: clarify the need for (added value of)

	this new systematic review given the publication of Huntley et al, 2013. - Methods: search – clarify what mean by a pragmatic update - Discussion: “There were limited data on the effect of CM on other health care resources. Observational intervention component data suggests that care providing family involvement and education/self-management are likely to be important in case management but these observations did not stand when subjected to subgroup analysis.” Given the results presented, these statements seem rather speculative. Either the evidence supporting these statements should be clarified or suggest drop.

REVIEWER	Ekaterini Lambrinou Department of Nursing, School of Health sciences, Cyprus University of technology
REVIEW RETURNED	24-Jan-2016

GENERAL COMMENTS	The authors performed a systematic review and meta-analysis in order to determine whether case management for patients with heart failure reduce unplanned hospital admissions. It is with pleasure I reviewed this useful manuscript. My comments for the manuscript: ABSTRACT 1. Methods used for the systematic review are not described (e.g. data sources searched, data selection method etc) 2. Primary outcome is different between the title and the abstract (Unplanned readmissions vs unscheduled secondary care). Unscheduled secondary care does not necessarily means readmission. 3. No quality assessment is referred. METHODS 4. Using the same terms always would make reading of the manuscript easier (e.g there referred eligibility criteria, inclusion and exclusion criteria – if there are not the same it is important for the readers to understand that and also be able to see them). 5. Why authors have not used the combination of the words used for the data search? Also, it is not clear how authors managed the whole amount of articles extracted. If papers in other language than English were extracted, how were they managed? 6. No quality assessment of the selected studies, or an assessment tool are referred. It is very important to have that in a systematic review and usually is based in the study design. 7. Figure 1 of the study selection is not referred on the manuscript. Also, it is suggested that it followed the PRISMA check-list which is not referred anywhere in the manuscript. 8. What it is also not shown to the present study is publication bias. I would suggest funnel plots and Egger’s test of asymmetry. Each study’s effect against its precision is shown through a funnel plot. Egger’ s test measures the funnel plot asymmetry by a linear regression approach. Furthermore, funnel plot’s results might suggest the need for a meta-regression analysis.

REVIEWER	Catherine Saunders RAND Eurooe, UK
REVIEW RETURNED	17-Feb-2016

GENERAL COMMENTS	This systematic review is clear, well written and of high quality. The methods are appropriate. I would recommend publication in BMJ Open. Please consider the following comments in preparing a revised manuscript: The review copy of figure 3 is unreadable – please could you send a high resolution version so that I can finish this review – incomplete comments are attached below. There is a very interesting discussion of secular trends in HF survival in the second paragraph of the introduction to this paper. Do any findings from this review (or the fact that included papers span 15+years) need some kind of discussion in the context of these trends? In Figure 1, why is there a difference between the n=183 records included after screening, and the 177 records where the full text was reviewed? It would be helpful to identify which of the studies included in this systematic review were also included in the previous systematic reviews (refs 9, 10) – and to clarify how this review is not the post-hoc selection of a single significant sub-group finding from the larger reviews in refs 9 and 10 which found no overall effect of case-management. In this paper there were a large number of sub-group analyses. Were these all pre-specified? How did you account for multiple testing? There are a large number of small trials in this review, which were potentially underpowered. Was there an assessment of publication bias in this analysis? For example, a recent review (here: http://www.bmj.com/content/352/bmj.h6817) comments that only about 20% of emergency admissions are preventable, and it is not clear how many events occurred in the intervention or control arms of the included trials during the follow up periods. Would it be possible to include the number of events in the intervention and control arms, as well as the rate ratios (for example in the tables in Appendix 2 – I suspect also in Figure 3). The outcomes in appendix 2 are also not clearly stated in the title or figures. With the length of stay outcome, was this length of stay for the hospital admission during which the HF cases were recruited to the case-management intervention, or LOS in one or all subsequent hospital admissions after the Case-Management intervention? These may have substantially different interpretations, and it would be worth clarifying how the outcome can be interpreted in this

	review.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
It is not clear why the authors have chosen to include non-RCT evidence (and the risk of confounding and selection bias) in their effectiveness review. A clear rationale needs for the inclusion of non-RCT needs to be provided.

Response
We choose to include both RCTs and NRCTs because we were particularly interested in the role of CM for HF in the community and we were aware that there was an evidence base of community based CM studies not all of which were RCTs i.e. RCT is evidence limited. We have added a sentence in the methods (eligibity criteria) to explain this.

Relatedly, there are two methodological problems with the current study as presented that need to be resolved. First, the Cochrane risk of bias tool is designed specifically for RCTs. The assessment of risk of bias/study quality of non-RCT should be assessed with an appropriate tool.

Response
We choose to use the standard Risk of score for RCTs for all as the review was dominated by RCTs but felt we had explained RoB across both study types clearly in results – however we agree we should have used EPOC RoB for the NRCTs and have done so in Figure 2b. We have amended the methods appropriately and feel the text in the results stands.

Second, it is not appropriate to combine evidence from RCT and non-RCT evidence. At the very least, the authors should stratify their pooling by study type and examine the variation in effect size by study type.

Response
Only one NRCT was included in the meta-analysis of hospital-initiated CM (Riegel 2000) and it was taken out in a sensitivity analysis along with a high risk RCT (Riegel 2002) and both data were reported. However we agree that this is not the best way to present the data. So we have made it clear in the text where the data has come from and have re calculated the relevant meta-analysis without the Riegel 2000 NRCT trial data included. We have retained the study name/data within the plot for completeness.
Removing Lowery (NRCT) from the meta-analysis left a n=2 for community-initiated CM so this is presented narratively only
These recalculations have no impact on overall conclusions.

The consideration of cost-effectiveness evidence is rather superficial in this review. Was a co-author a health economist or formally trained in economic evaluation methods? At the very least, the review should separate out the costs of the intervention, the costs of the downstream healthcare utilisation and (where reported) the incremental cost

Response
We agree that we have been brief in our reporting so we have included all cost data provided from the trials in one table (table 3) This shows the lack of, and heterogeneity of reporting of cost data from the studies. We discussed the potential need for a health economist for the review but agreed the data did not warrant the attention.

Abstract: clarify inclusion of both RCT and non-RCT evidence; give the total number of HF patients

included in the included trials by community and hospital based CM trials (also in results); as above, be more specific about “cost data”. Suggest reword conclusions to read “There were limited evidence for community-initiated CM reducing hospital admission”

Response
We have addressed all of these issues in the abstract and main text – thank you.

Introduction and discussion: clarify the need for (added value of) this new systematic review given the publication of Huntley et al, 2013.

Response

This is covered in detail in responding to comment 4 by reviewer 3. In brief, Huntley 2013 includes only CM for the older population. CM for HF patients was reported in a non-peer reviewed report available on line. The text has been edited to reflect this.

Methods: search – clarify what mean by a pragmatic update

Response
We meant that only the Medline search was re-run to update the review prior to submission not the other databases (due to time restraints). However the full search strategy was run again for the intervening time. The text has been edited to reflect this

Discussion: “There were limited data on the effect of CM on other health care resources. Observational intervention component data suggests that care providing family involvement and education/self-management are likely to be important in case management but these observations did not stand when subjected to subgroup analysis.” Given the results presented, these statements seem rather speculative. Either the evidence supporting these statements should be clarified or suggest drop.

Response

We have edited this statement. We felt it was of value to make as when we combined all studies containing family involvement it produced a significant rate ratio in favour of CM reducing admissions. However taking that analysis to its logical conclusion and comparing with studies of care with no family involvement the result was not statistically significant. We have been very careful in our wording not to overstate this observation and it is not in the abstract or concluding paragraph of discussion. See response to comment 5 by reviewer 3.

Reviewer: 2
ABSTRACT
1. Methods used for the systematic review are not described (e.g. data sources searched, data selection method etc)
2. Primary outcome is different between the title and the abstract (Unplanned readmissions vs unscheduled secondary care). Unscheduled secondary care does not necessarily means readmission.
3. No quality assessment is referred.

Response
1. Agree but the set headings of the abstract do not allow the details of the methods to be included.We are happy to confer with journal over this.
2. We have corrected this and been consistent with unplanned readmissions and LOS.

3. For the same reason as 1)

Using the same terms always would make reading of the manuscript easier (e.g. there referred eligibility criteria, inclusion and exclusion criteria – if there are not the same it is important for the readers to understand that and also be able to see them).

Response
we have been through the paper to ensure this.

Why authors have not used the combination of the words used for the data search?

Response

We devised our searches around CM as an intervention combined with patients with HF and study design. We did not limit the search by outcomes as we felt this approach was more inclusive at search level if different terms were used for admissions/unscheduled secondary care etc.

Also, it is not clear how authors managed the whole amount of articles extracted. If papers in other language than English were extracted, how were they managed?

Response

We did detail our strategy in the methods under eligibility criteria (p5/6). We did not need to proceed to full paper with any papers not in the English language. We have put a sentence in the results to reflect this.

No quality assessment of the selected studies or an assessment tool are referred. It is very important to have that in a systematic review and usually is based in the study design.

Response
This is on page 6. We have edited the title of the section to clarify this. Risk of bias results are on page 9.

Figure 1 of the study selection is not referred on the manuscript. Also, it is suggested that it followed the PRISMA check-list which is not referred anywhere in the manuscript.

Response
This is referred to after the first sentence of the results. (p7)
The PRISMA checklist was submitted with the article. We have added a sentence to the results to confirm this.

What it is also not shown to the present study is publication bias. I would suggest funnel plots and Egger's test of asymmetry. Each study's effect against its precision is shown through a funnel plot. Egger' s test measures the funnel plot asymmetry by a linear regression approach. Furthermore, funnel plot's results might suggest the need for a meta-regression analysis.

Response
Using Cochrane guidance we have not produced a funnel plot.

'Meta-analyses of risk differences are generally considered less appropriate than meta-analyses using a ratio measure of effect (see Chapter 9, Section 9.4.4.4). For similar reasons, funnel plots using risk differences should seldom be of interest. If the risk ratio (or odds ratio) is constant across

studies, then a funnel plot using risk differences will be asymmetrical if smaller studies have higher (or lower) baseline risk.'
However we have added a sentence to this effect in the discussion.

Reviewer: 3

The review copy of figure 3 is unreadable – please could you send a high resolution version so that I can finish this review – incomplete comments are attached below.

response
This was dealt with during the 1st peer review process but we have uploaded a high resolution copy in this response to reviewer's resubmission.

There is a very interesting discussion of secular trends in HF survival in the second paragraph of the introduction to this paper. Do any findings from this review (or the fact that included papers span 15+years) need some kind of discussion in the context of these trends?

Response
4 of the included studies were conducted in the 1990's, the remainder in the 2000's.
We have added a sentence or two in the discussion to link our results with this general trend. (2nd paragraph in discussion)

In Figure 1, why is there a difference between the n=183 records included after screening, and the 177 records where the full text was reviewed?

Response

This has been corrected. 183 full papers were screened. The error occurred due to taking qualitative papers out of included papers at the wrong level.(a qualitative paper has been prepared separately)

It would be helpful to identify which of the studies included in this systematic review were also included in the previous systematic reviews (refs 9, 10) – and to clarify how this review is not the post-hoc selection of a single significant sub-group finding from the larger reviews in refs 9 and 10 which found no overall effect of case-management.

Response
Our original research project was a large scoping systematic review of interventions to prevent admission and was published online as a report. (ref 10). From this report we prioritised specific topics based on expert and lay opinion, taking into account three published peer-reviewed papers of which one was Huntley A, 2013 (ref9) which covered CM for the general older population and did not include the heart failure studies. The published systematic review and meta-analysis of 11 RCTs showed that CM did not have an effect on admissions.
The data from 3 of 6 RCTs of CM for HF patients identified by the searches were subject to meta-analysis and this was written up in the report and suggested that for this specific patient group the evidence was promising (relative rate 0.61(0.44,0.85)). As data were limited this was not published as a peer-reviewed systematic review. Our current review was based on broader inclusion criteria with newer and more extensive searches and included 11 additional studies. We have added more detail in the text of the introduction to clarify this.

In this paper there were a large number of sub-group analyses. Were these all pre-specified? How did you account for multiple testing?

Response
In our protocol, which was not published we planned to 'identify the core components and setting of the case management interventions from the same studies.' Whilst we did specify we would conduct sensitivity analysis we did not specify the sub-analysis of the components. So we edited the text to describe these analyses as post-hoc analysis.

There are a large number of small trials in this review, which were potentially underpowered. Was there an assessment of publication bias in this analysis?

Response
See comment 8 above by reviewer 2

For example, a recent review (here: http://www.bmj.com/content/352/bmj.h6817) comments that only about 20% of emergency admissions are preventable, and it is not clear how many events occurred in the intervention or control arms of the included trials during the follow up periods. Would it be possible to include the number of events in the intervention and control arms, as well as the rate ratios (for example in the tables in Appendix 2 – I suspect also in Figure 3)

Response
.It is not technically possible to put these numbers into forest plots (produced by REVMAN) but we have added an extra column to table 2 (brief study description table) to add this information. We hope this acceptable.

The outcomes in appendix 2 are also not clearly stated in the title or figures.

Response
This has been corrected in the title of appendix 2 – all the data is unplanned readmissions

With the length of stay outcome, was this length of stay for the hospital admission during which the HF cases were recruited to the case-management intervention, or LOS in one or all subsequent hospital admissions after the Case-Management intervention? These may have substantially different interpretations, and it would be worth clarifying how the outcome can be interpreted in this review.

Response
The LOS data for CM-CHF initiated in hospital is for the readmissions. The data is presented in a variety of ways as it now possible to see in table 2 but the data used in the meta-analysis is all mean LOS in days.

VERSION 2 – REVIEW

REVIEWER	Rod Taylor University of Exeter Medical School
REVIEW RETURNED	12-Apr-2016

GENERAL COMMENTS	The authors have comprehensively responded to review comments and amended the paper such that it can be accepted for publication