Author's response to reviews

Title: Effects of Care Pathways on the In-Hospital Treatment of Heart Failure: A Systematic Review

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Version: 4 Date: 13 May 2012

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Effects of Care Pathways on the In-Hospital Treatment of Heart Failure: A Systematic Review

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Thank you for consideration of our manuscript for publication in your journal.
We have reviewed the above manuscript according to your reviewer's comments.

Reviewer: Ulrich Ronellenfitsch

Major Compulsory Revisions

Comment 1:
In the abstract, you should provide the reader with a brief introduction on what CPs are and how they could improve quality of care. Be aware that in the audience of a general medicine journal, not everybody is acquainted with CPs.

Answer: We agree with the comment and consequently we added the following sentence to the abstract “Care pathways (CPs) have become a popular tool to enhance the quality of care by improving patient outcomes, promoting patient safety, increasing patient satisfaction, and optimizing the use of resources”. (See text, page 3, first paragraph)

Comment 2:
In the first paragraph of the introduction, you refer to the cost of chronic heart failure and state that it is "almost the most costly chronic disease". It would be helpful to compare to the estimated cost of other diseases such as e.g. cancer.

**Answer:**
We agree, and indeed we added this sentence to the text on page 2
"The cost of HF care is two times higher than the cost of breast cancer, and three times higher than colorectal and lymphoma cancer care in the USA" (see text, page 2, first paragraph).

**Comment 3.**
While I fully acknowledge the amount of studies you have conducted and published in CP research, your paper would benefit from citing also key papers of other authors as this would avoid a unidirectional perspective on the matter. Likewise, already in the introduction you should specifically refer to studies evaluating effects of CPs for HF.

**Answer:**
We used other author’s paper as many as possible. But unfortunately there aren’t so many study groups working on care pathways.

**Comment 4:**
In the introduction, you mention that many hitherto conducted studies do not describe the intervention or context where CPs were introduced. How does your meta-analysis address this issue?

**Answer:**
We also think that this is a very important issue. As it was discussed previously discussed by Hawe (2004, 2007), implementation variation is inevitable but investigators still must be able to recognize and define the intervention integrity. That is why we mentioned this problem in our manuscript.

**Comment 5-A.**
Regarding your electronic search strategy, I am afraid it is not very sensitive. For example, you don't even use the term "clinical pathway". Usually, the Cochrane Collaboration stipulates a "highly sensitive search strategy", which I cannot find in your study. As asking you to modify your strategy at this point is not feasible, you should at least address this in the discussion.
We thank the Referee for his comment. For electronic search we used (‘clinical pathway’ OR ‘critical pathway’ OR ‘care map’ OR ‘clinical path’ OR ‘multidisciplinary approach’) words which are the same with “Effects of clinical pathways in the joint replacement: a meta-analysis” article of our study group which is similar to Cochrane search strategy was published in the Handbook. Because of a typing error in the submitted version we did not include “care pathways” key word. We apologize for that and the correct search strategy has now been presented in the text (See text, page 4, third paragraph).

Comment 5-B.
You consider a study as RCT if “it was specifically stated in the text”. Did you go into more detail and check if the respective studies were truly randomized, used allocation concealment etc.? Please give some details.

Answer:
We agree that this is could be a possible limitations. We went again through the papers but unfortunately in the texts no randomization method was explained in detail. It is mentioned in the discussion part no information was given about the randomization problem (page 12, first paragraph)

Comment 5-C.
According to predefined criteria, you should assign a quantifiable risk of bias to included studies. In a second step, I suggest conducting a sensitivity analysis which excludes studies with a low quality.

Answer:
We agree and according to the comment a sensitivity analysis has been performed and the results have been shown in the revised manuscript. Because of small number of the studies included we converted our publication as a systematic review and the result given are called as primary meta-analysis. No more statistical method was mentioned in the study.

Comment 5-D.
The a priori exclusion of articles without abstract might lead to missing eligible studies.
Answer:
We agree and we tried to reach abstract of these articles but unfortunately none of them were available in any of the database in Italian, Turkish or in Belgium national libraries.

Comment 5-E
Some authors suggest not to do pooled analyses if i-square is larger than 0.5. While I wouldn't be that apodictic, this issue should at least be addressed.

Answer:
We absolutely agree and we really appreciate this suggestion. We mentioned in the statistical analysis part about this problem. Page 7 first paragraph

Comment 5-F
Given your unclear selection criteria regarding the single studies' inclusion criteria (see comment 7), considerable heterogeneity between studies is to be expected. This heterogeneity exceeds what can be measured with age, sex and number of patients, parameters to which you refer in the discussion.

Answer:
We agree and we consequently revised our paper. The parameters which can result in heterogeneity have been discussed in the discussion section (See text, page 12, second paragraph)

Comment 6.
I suggest using a random effect model for all analyses, even if the i-square test is not significant. As you acknowledge yourself, there is a high probability of heterogeneity between studies because of context, different inclusion criteria for patients, learning curves etc. Since this heterogeneity is hardly measurable by objective indicators, the random effects model is more suitable.

Answer:
We agree and according to the suggestion we use the random effects model to analyze pooled results.
Comment 7.
I assume that HF can be defined in many different ways: chronic, acute, acute-on-chronic, severe, mild, life-threatening, to name just a few characteristics. I further assume that every single study has its own inclusion criteria, thus hampering comparability between studies and pooled meta-analysis. The validity of your results would strongly benefit from defining clear selection criteria for entering your meta-analyses, and from performing subgroup Meta-analyses

Answer:
We agree that this kind of detail would improve the validity of the results and the New York Heart Association classification would be the best way to perform subgroup analysis. Unfortunately only four of the seven studies reported NHYA classification and they didn’t give separate results for each classification. So unfortunately this not possible for this study but we will consider this advice for future planned meta-analysis for care pathways.

Comment 8.
Two of your outcomes should be better defined. First, up to which day is a re-admission considered as such? How is a re-admission for a different? Reason/diagnosis considered? Second, how do you define cost of treatment? As you know, there are many ways to calculate costs, which make comparison across studies difficult. Please re-run your analyses if needed.

Answer:
We agree but again not enough details were included in the original papers about the readmission time and cost calculation. To standardize cost estimations we actualized costs according to inflation rates.

Comment 9.
Reading the methods section, it does not become fully clear how you apply the EPA definition for in- or excluding studies into your meta-analysis. Please provide more details. Did you use some checklist or a similar tool? As far as I remember, the definition is more than just "a complex intervention [...] during a well-defined period", as you write in the introduction. Please give all relevant details.
**Answer:**
Defining characteristics (EFA definition) of care pathways include are given in the introduction paragraph. Also we developed a checklist to analyze the papers. Because it was not published we didn’t refer to this checklist.

**Comment 10.**
You state that "because it is not clear how the Kinsman et al. criteria for what is a CP were selected", you use the EPA criteria. Actually, Kinsman et al. made the effort to define their criteria through a standardized approach and to test it in a set of studies. In contrast, I was not able to find any clear explanation on how the EPA criteria were defined or validated. Can you give more information which explains why the EPA criteria should be more suitable for your study?

**Answer:**
The concern is absolutely justified In any case we also performed the selection using the criteria by Kinsman et al. All of the included study met also the criteria defined by Kinsman et al. Also Kinsman et al stated that “The definition promoted by the E-P-A is well-considered, accurate and inclusive” About the discussion on definition of care pathways a publication were referred in the discussion part

Vanhaecht K: Care Pathways are defined as complex interventions.

**Comment 11.**
Bearing in mind all the potential limitations of your study, I find that the statement made in the conclusions, which in a way assumes that the positive effect of CPs for HF has been unequivocally shown, is much too strong. Please rephrase that paragraph and explicitly mention the limited validity of your findings.

**Answer:**
We totally agree and we have accordingly substantially revised the paragraph: please see text, page 13, last paragraph, page 14 first paragraph.
Minor Essential Revisions

1. Use a unique terminology throughout the paper. In its current version, you refer to CPs both as "care pathways" and "clinical pathways".

   **Answer:**
   We agree and accordingly we used the term “care pathways”.

2. The last sentence of your abstract is not supported by your data. Besides, its language could be more scientific. Please rephrase or delete it.

   **Answer:**

3. In the methods, you state that the search was conducted for the period 1975-2010, whereas in the abstract it reads 1975-2007. Please correct the wrong date.

   **Answer:**
   It is corrected.

4. Were there any studies which were excluded because they did not comply with STROBE or CONSORT recommendations? If yes, give the respective numbers.

   **Answer:**
   We first checked the studies according to EPA characteristics any study met EPA criteria also comply with the most of the items in the STROBE or CONSORT.

5. Please describe the exact methods used for deducting the standard deviation from confidence intervals and for extracting data from graphs.

   **Answer:**
   Done

6. Please describe in more detail what the "mix data analysis program" does.

   **Answer:**
   We excluded analysis done in Mix software.

7. The last paragraph of the discussion is general reasoning unrelated to the results of your meta-analysis. Therefore, I suggest omitting it.

   **Answer:**
Reviewer: Jaime Peters

Major compulsory revisions

1. The authors should be careful about combining data from studies with very different designs. Different study designs are susceptible to different types of bias and confounding which, when combined, could provide misleading estimates of effectiveness. This does not seem to be discussed at all in the current draft, all study types seem to be assumed as being equivalent when this is clearly not the case.

Answer:
We performed sensitivity analysis to answer the question “Are the findings robust to the method used to obtain them? No evidence was observed. But number of the study isn’t enough to conclude evidence of bias or not. So results of sensitivity analysis weren’t included to manuscript. To eliminate effect of heterogeneity only random effect model was used. Also some characteristics which can result in heterogeneity discussed in discussion section.

2. I would not recommend reliance on trim and fill for detecting and adjusting for publication bias. This method, and in fact all methods, for detecting publication bias perform poorly when there are few studies in the meta-analysis and a great deal of heterogeneity exists as is the case here (see Terrin et al 2003 Statistics in Medicine 22 (p2113) or Peters et al 2007 Statistics in Medicine 26 (p4544) for interest).

Answer:
Because it is a systematic review anymore all detailed statistical part is excluded.

3. For instance, I disagree with the authors when they state that in the set of studies looking at mortality there is no evidence of publication bias. The fact that the largest study (which one could assume gives results closer to the true effect than the smaller studies, see definition of funnel plots in the Cochrane handbook) lies on the null effect and all other studies suggest a reduction in mortality might indicate that studies suggesting an increase in mortality may have been suppressed. Therefore, the overall estimate of 0.45 (0.21, 0.94) could well be an overestimate of the effectiveness. However, given that two of the five studies are
not RCTs and that there is such a large amount of heterogeneity between studies, makes an assessment of publication bias even more difficult (see point 1 above).

**Answer:**
Because none of the publication bias detection and correction methods aren’t reliable especially for small number of studies we changed our manuscript as systematic review. The result primary meta-analysis was given but no correction was done. And it is mentioned in the conclusion in future with more studies a meta-analysis should be performed.

4. The effect of publication bias is to overestimate the effect and research has found that results from observational studies tend to overestimate the results from RCTs. With both of these issues, and heterogeneity also present in some of the meta-analyses, I do not have much confidence in the author’s findings.

**Answer:**
Because care pathways for heart failure are implementations, none of the included study can be considered as an observational study. They are all clinical trials but some of them used historical controls. So they aren’t randomised controlled trials. Beside overall results we gave also subgroup analysis results for RCTs and CTs

5. Interestingly, there is greater heterogeneity between the three RCTs for the mortality outcome than when all 5 studies are considered and this needs some explanation.

**Answer:**
We added this sentence as an explanation in the discussion section.

“For the mortality outcome, there was greater heterogeneity between the three RCTs. This heterogeneity can be explained by small sample size and low mortality rate in CP group in Azad’s study”.

6. I do not understand why the authors had to make adjustments to the hospitalisation cost estimates to be able to synthesise them. Could they not have
used these data in their original format?

**Answer:**
Each study performed in different years and to eliminate effect of the inflation rate on costs, the costs were actualized.

7. In the main text there is little mention as to whether the care pathways or the populations included in the primary studies are at all comparable across studies (although there is some mention of this in the discussion section). Although the authors caution that care pathways are heterogeneous complex interventions, they could use this opportunity to try to tease out what aspects of care pathways or patient characteristics seem to lead to more effective results (i.e. attempt to explore the heterogeneity between studies). I would therefore recommend a more detailed Table 1 where, for instance, % male, mean age, severity level etc are reported for each individual study.

**Answer:** Concerning your advice %male and mean age were reported for each individual study in additional file 1

8. Related to this there is no mention of whether the primary studies undertook Sub-group analyses, findings from such analyses may help to explore some of the heterogeneity.

**Answer:**
Because of small number of the study were included, sub-group analysis were only performed according to experimental design. And no meta-analysis is available for care pathways with subgroups analysis for additional categories.

9. If the authors are only interested in whether care pathways, on average, are effective for HF patients, their current draft deals with this (noting above comments on the effects of publication bias and study design). However, would this be useful to readers? I think that a better paper could be drafted which at least attempts to explain some of the heterogeneity.

**Answer:**
Two paragraphs were added to discussion and attempted to explain reasons of some of the heterogeneity in the discussion part.
10. For quality assessment, the authors have used STROBE and CONSORT. These are guidelines for reporting, not for assessing quality. Checklists are available in the literature for assessing quality in RCTs and observational and would be much more appropriate for use.

**Answer:**
Corrected. Methodological quality of the included studies was assed using the Jadad methodological approach for RCT and CCT and the New Castle Ottawa Scale for the case-control studies, cohort studies and time interrupted series.

**Minor essential revisions**
11. Do not refer to ‘generic meta-analyses’, instead I believe you mean ‘meta-analyses of generic care pathways’?

**Answer:**
Care pathways are performed for a specific disease or treatment. But recently some authors combined results of many pathways for different disease. We refer these meta analysis to generic meta analysis.

12. Details on how the hospitalisation costs were dealt with are currently in the Section ‘Study inclusion/exclusion criteria’ (p5, lines 9-15) These should be moved to the Data Analysis Section.

**Answer:** Moved.

13. The section Outcome Measures repeats what is in the Study inclusion/exclusion criteria. I suggest deleting this information from the Study inclusion/exclusion criteria section.

**Answer:** Deleted

14. Capitalise MIX on p7 when describing how publication bias was assessed.

**Answer:**
Results of mix data analysis were excluded.

15. Give details as to how you got from 7981 records to 46 studies. Was this through screening of titles and abstracts?
   **Answer:**
   Please look at the data extraction and quality assessment section. There was a sentences “Two reviewers independently screened the titles, abstracts and keywords to identify eligibility and assessed methodological quality of the included studies and recorded the findings.” This sentences describes how we got from 7981 record to 46 studies.

16. In the results section, when referring to ‘significant’ results, make it clear that you actually mean ‘statistically significant’.
   **Answer:**
   Corrected both in methods and results.

**Discretionary revisions**

17. Although I no not know the topic area I would have thought that many readers would not need convincing that meta-analyses of generic pathways are not as good as those with are disease-specific. Therefore the authors cold probably delete the paragraph in the discussion justifying why meta-analyses of disease-specific care pathways are preferable.

   **Answers**
   We would like to keep this paragraph because we don’t think generic meta-analysis results can be generalized to a disease specific case. For further information; Vanhaecht K, Ovretveit J, Elliott MJ, Sermeus W, Ellershaw JE, Panella M: **Have we drawn the wrong conclusions about the value of care pathways? Is a cochrane review appropriate?**  Evaluation & the Health Professional 2011;doi: 10.1177/0163278711409209.
Reviewer: Larry Allen

Major compulsory revisions

1. The authors choose to focus this meta-analysis on heart failure. Given that heart failure is one of the most common reasons for hospitalization and readmission, this approach initially makes sense. However, the limitation to heart failure results in a very small collection of studies – only 3 which are RCTs – limiting the utility of performing a meta-analysis in the first place. Although I can understand that some of the aspects of care pathways for the care of patients hospitalized with heart failure with be unique to this disease process, there will also be many aspects of any care pathway that should cross various chronic disease states. Perhaps a better approach would have been to broaden the study of care pathways beyond heart failure to allow for restriction to higher quality data and to produce narrower confidence intervals. Please consider expanding the scope of this meta-analysis to care pathways in other chronic conditions.

Answer:

We performed disease specific meta-analysis to avoid possible problems of generic meta-analysis which was discussed in the discussion section. We don’t think generic approach can draw right conclusions about the value of care pathways.


Instead of performing a generic meta-analysis, we converted our study into systematic review by considering advice of BMC medicine editor.

2. Multiple study types were included such that the combined results are derived from both trail and observational data. First, don’t use “effect”, “impact”, and “improve” to describe associations at least partially derived from observational data. Second, the RCT data should typically be considered more likely to represent true “effect” based on the hierarchy of evidence. Among the 3 RCTs identified, the Philbin study is by far the largest (having more than double the
patient data than the other 2 trials combined). Looking through the figures and focusing on the RCT data, the results and conclusions in the abstract do not reflect the RCT data. For example, the Philbin article (largest RCT) has a RR of 0.99 for mortality (total RCTs 0.58 [0.23-1.43]), yet the conclusion of the article is that meta-effect of care pathways is 0.45 (0.21-0.94) – “clinical care pathways have a significant positive effect on mortality rate”. Furthermore, do the authors really think that implementation of care processes alone results in a more than 2-fold reduction in mortality? The length of stay data (Figure 4) is almost entirely observational. Please consider emphasizing RCT findings alone separate from the observational findings.

**Answer:**

Because care pathways for heart failure are implementations, none of the included study can be considered as an observational study. They are all clinical trials but some of them used historical controls so they aren’t randomised controlled trials. We classified all of the studies into two group; controlled or randomised controlled trials. In this version we gave also subgroup analysis results for RCTs and CTs.

We used increase and decrease instead of “effect”, “impact”, and “improve” to describe associations to avoid confusion. And RCT findings were considered alone separate from the CTs findings.

3. The authors say in the Abstract that “No significant differences were found in the rates of readmission and hospitalization costs.” However in the Results and in Figure 3, the meta-result is significant. Then the Discussion hedges saying that “readmission rate tends to decrease in the pathway groups”. Which is it? The data appears to be significant.

**Answer:**

Because of heterogeneity we applied random model and results are changed.

4. The authors perform statistical analyses to say that there is “no publication bias” but is there really power to make this statement? Please comment on the certainty with which these statements on publication bias can be made.
Answer:
We performed statistical analysis to detect publication bias. And no publication bias is observed for any of the outcome. Because of the small number of study included and none of the bias detection method is reliable especially for small number of study, in the revised version, we deleted statements about the publication bias.

MINOR ESSENTIAL REVISIONS:
5. The authors look back to 1975, but all of the studies included are from 1999-2008. Perhaps this date range should be emphasized, as I would question the validity of findings from care pathway studies from 25 years ago given the significant changes in care delivery and heart failure therapies over that time period.

Answer:
A sentence added to discussion part. “Another limitation of our study was that we searched from 1975 to 2010 but there wasn’t any eligible study until 1999. We can’t generalise our results for last 25 years but our study results is valid for last 12 years”.
(See text, Page 13, first paragraph)

6. Page 8 Results first paragraph: The authors say “and four cohort studies [39-41]” but I believe it should be three.

Answer:
Corrected.

7. Last additional file, Table 1: How can the Panella 2009 and Azad studies include patients with NYHA I? If patients are hospitalized for acute HF, then pretty much by definition they have symptomatic heart failure (non-NYHA I), yes?

Answer:
Panella 2009 wasn’t included NYHA I patients (corrected in additional files 2). But Azad used NYHA I (11 in control group and 12 in CP group). No explanation was done about the reason.

8. Pleural of female patients is “women” not “woman”.

Answer:
Corrected..

9. The writing is too informal at times. I am ok with first person or third person, but the use of second person “you may not…” is inappropriate.

**Answer**

Instead of you, “researchers” is used (See text, page 14, third paragraph).