PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Treatment targeted at underlying disease versus palliative care in terminally ill patients. A systematic review</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Reljic, Tea; Kumar, Ambuj; Klocksieben, Farina; Djulbegovic, Benjamin</td>
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</table>

VERSION 1 - REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Jørgen Hilden</th>
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<tbody>
<tr>
<td>University</td>
<td>Univ. of Copenhagen, Biostastics</td>
</tr>
<tr>
<td>REVIEW RETURNED</td>
<td>22-Feb-2016</td>
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</tbody>
</table>

GENERAL COMMENTS

This is an important review. It is only a pity that so few source studies were available. Methodologically the work keeps strictly to the Cochrane Collaboration guidelines and techniques, with the trustworthiness that follows. There are no obvious missed opportunities for supplementary analyses.

My remarks will therefore mostly deal with minor details. References px/y are to Authors’ pg no x, pdf line no y. PC = palliative care, TTD = active treatment of disease.

Minor matters
A1) P2/42, “OS”: please check that abbreviations are explained.
A2) P1/18: Tampa.
A3) In the Table, line 3 (just under “Risk with PC”) stands the word “Moderate” – which I don’t understand.

Presentation
B1) P2/43: “does nor impact” as a highlighted conclusion following a non-significant key comparison invites a comment. I would prefer the wording “did not demonstrably impact.” In the Title, past tense (“did not”) would in fact also be appropriate; but there is a tradition, I think, for being informal in that type of Conclusion-in-Title title.

B2) The table: please make sure the direction of the trends is unambiguous. I suggest you change the wording in the ** footnote on p11/18 into:

- < 1: poorer results with PC; > 1: poorer results with TTD, … …

Next I suggest that all the clinical labels in the front column are given same (unfavorable) direction: to achieve this, it suffices to change the top entry, “Overall survival (OS)”, into “Overall mortality [rate]”. It then becomes more obvious that there are three and only three
features where PC performed more poorly than TTD, viz. overall mortality, treatment-related mortality(!), and abdominal pain (though none of them reaches statistical significance).

B3) In Fig 2 (Forest plot of overall survival), the interpretation of right and left is clearly marked under the graph. One may repeat it in the legend. Also, one may prefer to call the figure a “Forest plot of overall mortality”.

Suggestions
C1) The authors excluded trials comparing palliative care (PC) as an add-on in trials in which two active treatments (TTDs) were compared (p4/44). Is there some supplementary insight buried here?

C2) Prompted by p5/19, ‘palliative radiotherapy’: the logic of the scientific question before us demands that all anti-neoplastic measures should count as TTDs. When (a variant of) radiotherapy is regarded as a purely palliative measure, it requires a clearly stated motivation. Or else some reader might ask, “Chemo XYZ also has almost no side-effects and relieves cancer pain; why do you regard XYZ as a TTD?” Where exactly is the critical dividing line between palliation and more-than-palliation? (It is hardly enough to say that it depends on the prescribing doctor’s intension – or else palliative vs. more-than-palliative intension should be an explicit part of the aim of the project.)

C3) The title correctly portrays the aim of the systematic review. However, as all the useable source studies turned out to deal with oncological patients, one may consider smuggling the word ‘cancer’ into the title (adding an apology for this post-hoc change of scope in the Introduction and/or Methods section).

C4) A related problem might deserve mention (although I appreciate that the manuscript bypasses all questions of professional conduct and duties and sticks to objective aspects). Kaija Holli (Tampere, Finland) has had a life-long interest in overuse of not only TTDs but also diagnostic tests in the last couple of months or even weeks of breast cancer patients’ lives. Inconsequential lab tests and X-rays are no doubt ordered just to do something (and to avoid having to speak of the inevitable). I was shocked when I saw her figures in 1988 (see Holli & Hakama, BMJ 1989,298,13-14), but the ones her group produced later were almost as bad (Asola, Huhtala & Holli, Breast Cancer Res Treat 2006,100,77-82).

REVIEWER
Charles Bennett
University of South Carolina

REVIEW RETURNED
08-Mar-2016

GENERAL COMMENTS
This is a nice article.
Lamont and Christakis indicate that MDs are poor in selecting
persons with 6 months or less of life. Hence it is difficult to appropriately triage persons into the palliative care vs the treatment group. I also found that the palliative care group should have had more n/v with narcotics. I think that the paper strongly calls for a RCT in the current era.

Some estimate about how frequent the toxicities are in the treatment group are would be of interest.

Some mention of the results of the large trials would be of interest.

A less strong conclusion might be considered—calling for an RCT for example.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name: Jørgen Hilden
Institution and Country: Univ. of Copenhagen, Biostatistics, Denmark Competing Interests: None declared

Review of BMJ Open ms 2016-011464,
“Active treatment in the end-of-life setting does not prolong survival … Systematic Review” by T. Reljic & al.
February 19, 2016 / Jørgen Hilden (Copenhagen)

This is an important review. It is only a pity that so few source studies were available. Methodologically the work keeps strictly to the Cochrane Collaboration guidelines and techniques, with the trustworthiness that follows. There are no obvious missed opportunities for supplementary analyses.

My remarks will therefore mostly deal with minor details. References px/y are to Authors’ pg no x, pdf line no y. PC = palliative care, TTD = active treatment of disease.

Minor matters
A1) P2/42, “OS”: please check that abbreviations are explained.
Response: Abbreviation added. Thanks!

A2) P1/18: Tampa.
Response: Changed. Thanks!

A3) In the Table, line 3 (just under “Risk with PC”) stands the word “Moderate” – which I don’t understand.
Response: We have now removed the term “Moderate” from the Table in order to avoid confusion which is the default mode with GRADEPro software. Thanks!

Presentation
B1) P2/43: “does nor impact” as a highlighted conclusion following a non-significant key comparison invites a comment. I would prefer the wording “did not demonstrably impact.” In the Title, past tense (“did not”) would in fact also be appropriate; but there is a tradition, I think, for being informal in that type of Conclusion-in-Title title.
Response: The conclusion now reads “did not demonstrably impact.” Thanks!

B2) The table: please make sure the direction of the trends is unambiguous. I suggest you change the wording in the ** footnote on p11/18 into:

< 1: poorer results with PC; > 1: poorer results with TTD, … …

Next I suggest that all the clinical labels in the front column are given same (unfavorable) direction: to achieve this, it suffices to change the top entry, “Overall survival (OS)”, into “Overall mortality [rate]”. It then becomes more obvious that there are three and only three features where PC performed more poorly than TTD, viz. overall mortality, treatment-related mortality(!), and abdominal pain (though none of them reaches statistical significance).

Response: The primary endpoint of this systematic review as pre-specified in the protocol is overall survival (time-to-event outcome). Accordingly, when possible, the data were collected as hazard ratios from original studies therefore we do not know the total number of mortalities on each arm and cannot accurately report the overall mortality. Since all of the results are not in the same direction (i.e. survival is favorable, adverse event is unfavorable) we have maintained the wording as “effect” size rather than “poorer results”.

B3) In Fig 2 (Forest plot of overall survival), the interpretation of right and left is clearly marked under the graph. One may repeat it in the legend. Also, one may prefer to call the figure a “Forest plot of overall mortality”.

Response: We have now added the labeling in the legend. We maintain the tile “Forest plot of overall survival”. Please see response to B2.

Suggestions
C1) The authors excluded trials comparing palliative care (PC) as an add-on in trials in which two active treatments (TTDs) were compared (p4/44). Is there some supplementary insight buried here?

Response: This is an interesting question however it was outside the scope of the current review. Our primary aim was to compare the continued use of TTD versus discontinuing TTD and using only PC in management of patients at the end of life. Thank you!

C2) Prompted by p5/19, ‘palliative radiotherapy’: the logic of the scientific question before us demands that all anti-neoplastic measures should count as TTDs. When (a variant of) radiotherapy is regarded as a purely palliative measure, it requires a clearly stated motivation. Or else some reader might ask, “Chemo XYZ also has almost no side-effects and relieves cancer pain; why do you regard XYZ as a TTD?” Where exactly is the critical dividing line between palliation and more-than-palliation? (It is hardly enough to say that it depends on the prescribing doctor’s intension – or else palliative vs. more-than-palliative intension should be an explicit part of the aim of the project.)

Response: We understand this concern. Please note that, we went by the intent (palliative versus TTD) of the study investigators as stated in the introduction section as objectives, methods section under the primary and secondary outcomes, and discussion section of the manuscript. We have now explained this in more detail in the eligibility criteria. This data was extracted in duplicate for all included studies as well as was part of the study inclusion criteria. Thank you!

C3) The title correctly portrays the aim of the systematic review. However, as all the useable source studies turned out to deal with oncological patients, one may consider smuggling the word ‘cancer’ into the title (adding an apology for this post-hoc change of scope in the Introduction and/or Methods section).
Response: We have changed the title to comply with the BMJ Open standard of not using declarative titles. However, we have chosen to maintain the words “terminally ill patients” because it reflects the work that was performed. We did review all disease literature however only cancer studies met the inclusion criteria. We made sure that this was made clear in the abstract by reporting “All RCTs included cancer patients” as well at Table 1. Therefore it should be easy to search and index.

Thanks!

C4) A related problem might deserve mention (although I appreciate that the manuscript bypasses all questions of professional conduct and duties and sticks to objective aspects). Kaija Holli (Tampere, Finland) has had a life-long interest in overuse of not only TTDs but also diagnostic tests in the last couple of months or even weeks of breast cancer patients' lives. Inconsequential lab tests and X-rays are no doubt ordered just to do something (and to avoid having to speak of the inevitable). I was shocked when I saw her figures in 1988 (see Holli & Hakama, BMJ 1989,298,13-14), but the ones her group produced later were almost as bad (Asola, Huhtala & Holli, Breast Cancer Res Treat 2006,100,77-82).

Response: This is indeed very interesting. We will consider it in the future. Thanks!

Reviewer: 2
Reviewer Name: Charles Bennett
Institution and Country: University of South Carolina, USA Competing Interests: none

This is a nice article.
Lamont and Christakis indicate that MDs are poor in selecting persons with 6 months or less of life Hence it is difficult to appropriately triage persons into the palliative care vs the treatment group. I also found that the palliative care group should have had more n/v with narcotics. I think that the paper strongly calls for a RCT in the current era.

Response: We fully agree. Thanks!

Some estimate about how frequent the toxicities are in the treatment group are would be of interest.

Response: The estimated frequency of reported toxicities is reported under “Anticipated absolute effects”, “Risk with TTD”. Unfortunately, data was not available for patients with any adverse event. Since multiple events could happen in a single patient, we were unable to generate this outcome by adding individual toxicities together. Thanks!

Some mention of the results of the large trials would be of interest.

Response: We have not done this since the goal of systematic review and meta-analysis is to incorporate all known evidence. Focusing on the results of a couple of larger studies and ignoring the entirety of evidence would go against this principle. Thank you!

A less strong conclusion might be considered-- calling for an RCT for example.

Response: We have now reworded the conclusion to be less strong and included some recommendations on future research needs. Thanks!
VERSION 2 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Jørgen Hilden</th>
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<tbody>
<tr>
<td></td>
<td>Univ. of Copenhagen, Biostatistics</td>
</tr>
<tr>
<td>REVIEW RETURNED</td>
<td>12-Oct-2016</td>
</tr>
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</table>

| GENERAL COMMENTS  | The revised text is unobjectionable. The authors’ reactions to the two reviewers are clear and plausible. [However, I cannot help saying that Table 2 has too many decimals in some places (see leuko/neutropenia results); the width of a confidence interval will itself indicate how many digits it is meaningful to have in its end points!] |

VERSION 2 – AUTHOR RESPONSE

With respect to the reviewer’s comments, we acknowledge the very wide confidence intervals for the outcomes of Leukopenia and Neutropenia. However, we have chosen to keep all of the outcomes in the manuscript in the interest of full reporting. The quality of evidence for these outcomes has been downgraded according to GRADE recommendations.
Treatment targeted at underlying disease versus palliative care in terminally ill patients: a systematic review

Tea Reljic, Ambuj Kumar, Farina A Klocksieben and Benjamin Djulbegovic

BMJ Open 2017 7:
doi: 10.1136/bmjopen-2016-014661

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