Author's response to reviews

Title: Unbearable suffering and requests for euthanasia prospectively studied in end-of-life cancer patients in primary care

Authors:

Cees DM Ruijs (c.ruys3@kpnplanet.nl)
Gerrit van der Wal (g.vanderwal@vumc.nl)
Ad JFM Kerkhof (ajfm.kerkhof@psy.vu.nl)
Bregje D Onwuteaka-Philipsen (b.philipsen@vumc.nl)

Version: 2 Date: 9 November 2014

Author's response to reviews: see over
Dear editor,

Thank you for providing us the opportunity to react to the comments of the reviewers and for providing extra time before resubmitting. We present a revised article, with the above name, in which the comments to the reviewers have been addressed. You will also find attached a point-by-point response to the comments of the reviewers.

Sincerely,
Also on behalf of my co-authors,
Cees Ruijs

POINT-BY-POINT RESPONSE TO CONCERNS:

Editorial Comments:
Thank you for submitting your manuscript to BMC Palliative Care. The comments of the reviewers who reviewed your manuscript are included below. Please address each comment when preparing your manuscript for resubmission.

*1. Introduction is thorough, too much so. It's much too broad in my mind and could be boiled down to only the essential, shortly describing 1) difficulties for physicians in assessing and responding to suffering; 2) unbearable suffering as central criterion, among others, for assisted dying in most jurisdictions where it is legal - focussing only or primarily on the NL where this study is set; 3) running through the numbers of EAS (requests), in cancer patients and primary care, to set the stage and to show that your patient subset is the group best represented in EAS statistics. I don't even know what the significance of the second last paragraph is.

Answer: The Introduction (page 3) has been shortened according to the comment. In the first paragraph the criterion of unbearable suffering amongst others is presented (page 3, sentence 2-11). In the second paragraph the numbers are presented according to the comments (page 3, sentences 12-23). Finally, in the third paragraph the difficulties for physicians in assessing and responding to suffering are presented (page 3, sentences 24-29).

*2. Methods, measurement instrument, extra qualitative assessment of unbearability: can you give more insight and explain in more detail how you qualified/deduced unbearability from this
information? Was it used to rule it out or to confirm or both? And who decided on this? Further in the analysis paragraph I saw that this qualitative assessment doesn’t feature in your operationalisation of unbearable? Important questions given it is central to the paper.

Answer: The methods and the rationale behind the methods have been explained in more detail. First, under the heading ‘Issues concerning the investigation of unbearable suffering’ the issues that need consideration in measuring unbearable suffering are discussed more in general. (page 4, sentences 24-43; page 5, sentences 1-13).

This is followed by the heading ‘Measurement instrument: the State-of-Suffering V’ in which the SOS-V, the instrument in which the above mentioned considerations are taken into account is described more clearly now (page 5, sentences 15-40). Then, in the next heading the analysis is more explicitly presented (page 5, sentences 42-45; page 6, sentences 1-20), also for the qualitative analysis.

By the revision it has become more clear that the patients qualified unbearability through providing scores for unbearable suffering, and that in the qualitative assessment the qualitative descriptions provided by the patients for symptoms which were scored unbearable are categorized according to type of suffering. In addition, in Box 1 (page 20) a third row has been added, which provides examples of the assessment process; in this way the categorization process is made visual and understandable for the reader.

Related to the previous question: can you explain a bit more your rationale for equating a (very) serious symptom with unbearability? It may be a bridge too far to deduce the impact of a symptom from its severity...or is it here that the qualitative assessment comes in? Some symptoms can be extremely severe yet bearable for the patient, and vice versa.

Answer: With the clearer description of the SOS-V (see previous comment) we have made clear that indeed we distinguish between presence or intensity of a symptom and extent to which it is considered unbearable by a patient.

There’s an entire conceptual discussion about unbearability, as the authors undoubtedly know. As you see, a bit more clarity could be provided around the operational definition of unbearability.

Answer: For purpose of providing clarity we present and discuss suffering, the domains in which suffering may occur, categories of suffering and overlap which may occur between categories of suffering (Methods, page 4, sentences 24-43; page 5, sentences 1-13). The operationalization of suffering is clarified through describing the measurement process (Methods, page 5, sentences 25-37) and the process of analysis (Methods, page 5, sentences 42-45; page 6, sentences 1-20).

3. The study has a low number of cases (n=17 & 47):

* important to warn reader that statistical power is limited and the lack of significant differences does in this case certainly not mean that there are no differences between groups. Because of the low number of cases, not many significant factors were found to discuss, even the ones in the literature associated with requesting EAS (loss of control,etc). This underscores my comment that it is very difficult to show or disprove things with limited statistical power. Though it is mentioned in the limitations section, the authors should definitely make it clear in the discussion that the absence of
Significant findings in no way show that the studied factors are irrelevant (as it could be read by less knowledgeable readers).

**Answer:** The limitation related to the low numbers has been more explicitly presented (Discussion, limitations-section, page 8, sentences 24-26): “The present study has some limitations. The first is the limited number of patients, which limits statistical power. We cannot rule out that there are differences in unbearable suffering between patients with and without an explicit request that we did not find.”

Even the conclusion that unbearable suffering is "not the dominating motive differentiating for either or not requesting EAS" may be presumptuous.

**Answer:** The conclusion has been reformulated and is now presented more cautiously. Yet, the finding is remarkable and requires to be mentioned. E.g. if unbearable suffering is a strongly differentiating factors, than with relatively low numbers significance could have been achieved.
- Discussion, page 7, sentences 28,29: “These findings may indicate that unbearable suffering is not the dominant motive to request EAS.”
- Discussion, page 8, sentences 37,38: “The study raises the question of whether unbearable suffering is the dominant motive to request for EAS.”
- Abstract, page 2, sentences 29,30: “The study raises the question of whether unbearable suffering is the dominant motive to request for EAS.”

Partly as a result of this, the discussion lacks 'punch' in general.

**Answer:** To provide more punch, paragraphs which were not strictly necessary were left out of the discussion. Such accounts for:
- Discussion: paragraph 6 of the former submission: Reasons why suffering patients do not request EAS: this was not a subject of investigation: it is now left out
- Discussion: paragraph 8 of the former submission: A conceptual model of balance of interacting factors: this was not subject of investigation and has been left out.

To provide more punch the titles was reformulated: the essence of the study was concentrated in the first 6 words of the titles: “Unbearable suffering and requests for euthanasia ………”

Perhaps the authors could consider additional analyses, some of which I propose under ‘discretionary revisions’ (points 12-15).

* If significant differences are found with such low numbers there is likely a strong connection with the significant variable and can be highlighted.

**Answer:** No significant differences were found: Results, page 6, sentences 40-45, page 7, sentences 1,2: “No significant differences …… unbearable symptoms per domain”

* prevalence calculations are untrustworthy and this should be mentioned.
Answer: We are not sure what the reviewer precisely means. It is known that open, non-systematic questioning about symptoms will result in assessed prevalences which are too low. This is pointed out in the article: Methods, page 4, sentences 31-32: “Evaluation of unbearable suffering in relationship to specific disease indicates a systematic investigation of whether disease specific symptoms are present [26-29], followed by an assessment of whether symptom related unbearable suffering occurs.”

In the present study systematic questioning was used, with the objective to prevent untrustworthy outcomes of prevalences. This is pointed out: page 5, sentences 20-21: “Cancer is polysymptomatic and systematic assessment of symptoms is indicated”; and: page 5, sentences 23-24: “The SOS-V systematically addresses 69 symptoms”

*4. I also think the Discussion section could be streamlined a bit more contentwise. For instance, paragraph 7 (underlying message of a request) could be combined with paragraph 2 (performance in 1/3), linked as an explanation for non-performance (maybe you can do the same with paragraph 9 (physician responses)). Otherwise, it’s difficult to see the direct connection with your study results.

Answer: We agree that the Discussion could be more streamlined. Given the focus of our article on motives for requests for EAS, we have chosen to ball paragraph 4 (“Control”, “Other motives to request EAS”) and paragraph 5 (“A genuine desire to die may be absent”) of the former submission into one new paragraph (now paragraph 3 of the Discussion) about other reasons than unbearable suffering which may drive a request for EAS: Page 7, sentences 40-45 and page 8, sentences 1-10: “Motives for EAS may need to be interpreted from a different perspective. A ……… of provision of care [3,19,66,68,69].” The significant differences found in this study concerning presence of advance pro-euthanasia directive, and higher education, in relationship to either or not requesting EAS, were interpreted within this new paragraph (page 8, sentences 10,12): “The presence of an advance ……… of choice”

Performance and non-performance were not added to this paragraph, because this concerns the response of a physician, which was not the focus of this study.

The paragraph 2 (performance in 1/3) of the former submission has been transferred to paragraph 1, where it is discussed that the findings for the issue of either or not performing EAS in response to an explicit request are comparable to other studies in the same setting: page 7, sentences 15,16: “EAS in one out of three patients with an explicit request for euthanasia is comparable to findings in other studies in the Dutch setting [10,11,49,50].”

Paragraph 9 (physician responses) of the former submission in the present article is paragraph 4, which in connectedness logically follows paragraph 3. Page 8, sentences 13-27: “Patients depend upon …… to perform euthanasia [74]. “

Also, you could ball all possible motives for an EAS request (all of which were not significantly different in your study) into one paragraph.
Answer: All possible motives for an EAS request, which were not found to be significantly different in this study, have been balled together in one paragraph (paragraph 2 of new submission): page 7, sentences 21-29 : “No differences occurred ....... not the dominant motive to request EAS”.

Maybe also one paragraph with strengths (incl. originality of your research, what your study adds) and limitations together.

Answer: Strengths of the study were not mentioned in the former submission, nor originality. The present study in a prospective, patient directed designs investigates differences in the motive of unbearable suffering related to either or not requesting EAS is a setting where EAS legally is permitted. We have added strengths and what the study adds, which has been added immediately to the first paragraph of the Discussion, to be clear about the fundamental issues at stake (and thus provide more punch to the article): page 7, sentences 16-20: “A particular strengths of this study is its originality. Through prospective, patient directed research, it touches on fundamental questions about suffering, life and death, autonomy and the question of the tasks of the medical profession. We have not identified prior prospective patient directed studies investigating unbearable suffering in relationship to EAS.”.

Minor essential revisions
*5. Number of independent tests is high, Bonferroni correction should be applied to p-values of the symptom tests.

Answer: The Bonferroni correction has been applied, after which no significant differences related to the SOS-S symptoms remained:
-Methods, page 6, sentences 10,11: “Additionally Bonferroni analysis for high numbers of independent tests was applied”
-Results, page 6, sentence 43: “however after application of the Bonferroni correction no significant differences remained.”

*6. I found some typo's, language could be clearer, and grammar is off sometimes. The manuscript would certainly benefit from review from a native speaker.

Answer: the manuscript has been revised by a native English speaker

*7. Methods, analysis, second paragraph: “Only one rating per unbearable answer was permitted: the best fitting match.” is all a bit confusing at this point. I presume you mean only one rater’s score (on whether or not a symptom was unbearable) was used, ie the one best fitting with what? Please clarify.

Answer: The text has been adapted:
-First: it is explained more explicitly that it is the patients rating which determines unbearability: Methods, page 5, sentences 29,30: “When a patient rates 4 or 5 for unbearable suffering, the experience is further explored through open ended questions”.
-Second: Methods, page 6, sentence 19: “One rating per unbearable description was permitted”
-Third: examples of the categorization process have been added: page 20, box 1, third column.
*8. Results: from Table 2 onwards you only have 60 instead of 64 patients. What happened to the 4 missing patients? Did they not complete the SOS-V? Maybe I missed it somewhere, but it should be mentioned.

**Answer:** The information has been made more explicit:
- Abstract, page 2, sentences 21-22: “in four patients the SOS-V was missing”
- Methods, page 4, sentence 16-18: “In 60 patients at least one SOS-V interview was present; in four patients the interview was missing; the interviewer had considered the interview too burdensome and abandoned.”
- at bottom of tables 2,3,4 (pages 16,18,19): “The SOS-V was missing in four patients”

**Discretionary revisions**

*9. Abstract, background: last sentence is not necessary.

**Answer:** The last sentence was too generally formulated; it has been changed. The concerning outcome is interpreted in relationship to the compulsory criteria: Abstract, page 2, sentences 30-33: “Most patients suffered from unbearable symptoms, indicating that the compulsory criterion of unbearable suffering, may be met a priori in most end-of-life cancer patients dying at home, whether they request EAS or not. “

*10. Abstract, methods: ‘bimonthly’ could mean both 2x per month and every 2 months. Better to say ‘every two months’.

**Answer:** Such has been done:
- Abstract, page 2, sentence 14:” Every two months suffering was assessed with the State-of-Suffering V (SOS-V)”
- Methods, page 3, sentence 41 :” Follow-up interviews were administered every two months”.

*11. Methods, first paragraph, last sentence. Can you say something more about which clinical signs were used and who interpreted them?

**Answer:** Rapid deterioration of the condition of end-of-life cancer patients in the ultimate phase is a serious threat to patient recruitment. Timely recruitment is advised.
The GPs estimated survival. Clinical signs which reliably predict survival do not exist. To explain this in more detail would result in unnecessary lengthening of the article. We changed “within six months” to “within half a hear”, thus referring to al less precise estimation.

The text has been adapted;:
-Methods, page 3, line 34: “expected do die within half a year”

This matter has been addressed in a previous article about patient recruitment, to which a reference is provided in the article: page 4, sentences 6,7: “The recruitment process is described in detail elsewhere [24]”

*12. Do the authors have information on when in the final 6 months the EAS request was posed? If so, wouldn’t it be better to use the SOS-V symptom scores of the data point immediately after the request? We know symptoms and their unbearability can fluctuate over time, so why not use the data point closest to the request? I understand that this would mean you are then not using the same data points as those for patients without a request, but it would be all the stronger if you could show that when a patient requests EAS, some symptoms are more severe than in patients at the very end of life not requesting EAS.

Answer:
-There was no information about the date of the request: Methods, page 3, sentence 45: “to record the date of the request was not part of the study design.”.
-It is relevant that EAS in majority concerns the ultimate two weeks of life: Methods, page 5, sentences 43-45: “Only the final SOS-V interviews were analyzed, being the interviews closest to death, taking in account that performing EAS in response to an explicit request in majority occurs in the ultimate two weeks of life [10,13].”
-When EAS is not performed, this may frequently also be close to the moment of death: Discussion, page 7, sentences 35-39: “Identified causes of ungranted requests for EAS included death of the patient before performance of EAS (20%; percentage of total of ungranted requests), death of the patient before finalization of decision making (20%), withdrawal of the request by the patient (20%) and refusal of the physician to comply to the request of the patient (18%) [49].”
-The study design was directed at realizing interviews shortly before deaths: Methods, page 3, sentences 41,42: “Follow-up interviews were administered every two months, or sooner based upon information by GPs that the condition of a patient had rapidly deteriorated”.
-This did not work out as designed: Results, page 6, sentences 30-33: “A part of the study design was to obtain information from GPs that the condition of a patient had rapidly deteriorated, so that additional interviews could be planned close to death. This however, hardly occurred.”

*13. Did the authors think of studying differences in evolution of symptoms between patients with and without a request, taking into account when the requests were made? Though complicated, some techniques are available to do this. Now you are not exploiting the longitudinal character of the survey.

Answer: the number of patients with more than one interview was lower than the number of currently analyzed patients, which would limit statistical power. The number of patients with at least
two interviews is presented: Methods, page 4, sentence 18: “In 33 patients the SOS-V was administered at least two times.”

*14. Results: so many items on the SOS-V scale; did the authors consider grouping them together according to larger, internally consistent categories (ideally via factor analysis or consensus-based thematic grouping) to reduce the number of items, especially considering there are virtually no significant differences in individual items?

**Answer:**
- Additional analysis for numbers of unbearable symptoms per domain were performed, which were not significant: Results, page 7, sentences 1,2: “There were no differences in numbers of unbearable symptoms per domain.”
- To reduce the number would result in missing relevant information, considering the subject of this study: Methods, page 5, sentences 33-34: “Reduction of data assessed with the instrument was not striven for; the symptoms are clinically differentiable and any symptom may determine unbearability.”

*15. Discussion: Your paragraph about balance of interacting motives: this is something you can check with your data, if you test for differences in combinations (or simply the number) of unbearable symptoms.

**Answer:** We mentioned a balance of interacting actors which stimulate or inhibit the wish to continue living; this would require presence of actors with positive as well as actors with negative effect to check the hypothesis. Stimulating actors to the wish to continue living were not studied, so this issue cannot be studied from the perspective of the present study. The balance chapter was taken out; for further information read under comment nr. 4.

*16. I think the findings could be very different in non-cancer patients. Perhaps this is worth a recommendation for future research as well? What do the authors think?

**Answer:** this certainly is an interesting comment. Taking in account the relatively low prevalence of non-cancer patients with explicit requests for EAS, and considering the difficulty to realize a sufficiently large population in the present study directed at a population with a relatively high prevalence, reasons occur which result in a question whether such an advice relates to feasible research. We decided for the moment to refrain from such an advice.

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.