PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Multicomponent non-pharmacological intervention to prevent delirium for hospitalised people with advanced cancer: study protocol for a phase II cluster randomised controlled trial
AUTHORS	Hosie, Annmarie; Phillips, Jane; Lam, Lawrence; Kochovska, Slavica; Noble, Beverly; Brassil, Meg; Kurrle, Susan; Cumming, Anne; Caplan, Gideon; Chye, Richard; Le, Brian; Ely, E. Wesley; Lawlor, Peter; Bush, Shirley H.; Davis, Jan Maree; Lovell, Melanie; Brown, Linda; Fazekas, Belinda; Cheah, Seong; Edwards, Layla; Agar, Meera

VERSION 1 – REVIEW

REVIEWER	Tammy Hshieh Brigham and Women's Hospital; Dana-Farber Cancer Institute, USA
REVIEW RETURNED	14-Sep-2018

GENERAL COMMENTS	This paper addresses an important and interesting topic in delirium that remains incompletely answered. Specifically, whether patients with advanced cancer would benefit from multicomponent non-pharmacological intervention to prevent delirium. The methodology of these authors in designing and evaluating a clinical program to do so is thoughtful and robust. I look forward to reading about the results of this study, and the subsequent multi-site phase III cluster RCT if this one deems it feasible. I am a bit disappointed that delirium incidence and severity are only secondary outcomes in this current study but understand that adherence is the primary question here. I wonder if delirium incidence and severity should potentially be considered primary outcomes. Previous multicomponent interventions, as discussed by the authors on Page 5 did not show an impact on delirium but the authors are able to clearly explain limitations and issues with that study. If this current ambitious study demonstrates good adherence but no impact on delirium, though, would a Phase III trial necessarily be executed? Finally, I definitely see the merits of multicomponent delirium intervention in advanced cancer patients but the authors raise the concern that others may not appreciate this study on page 8 ("delirium may be considered innocuous in advanced cancer and palliative care contexts ... preventing delirium is not possible, necessary or likely to be effective.") But the authors to not address why they disagree. It would strengthen the introduction for the authors to address these limitations (of perception by others) directly.

REVIEWER	Asao Ogawa

	National Cancer Center Hospital East, Japan
REVIEW RETURNED	17-Sep-2018

GENERAL COMMENTS	Dear authors, Thank you very much for this interesting and exciting work I was able to review. For the better understanding of your study, I have some questions: 1. A multicomponent non-pharmacological intervention is important for preventing delirium in people with advanced cancer. In general strategies for preventing delirium in general hospitals, the interventions involves careful pain control, and avoiding polypharmacy. Maybe it would be better to add the discussion of selecting 5 components. 2. In the people with advanced cancer, the factors promoting delirium vary a great deal and some factors are out of control. From the perspective of practice, the data of psychoactive medication and opioids is informative to assessing the behavioral modification of the clinical teams.

REVIEWER	Karolina Piotrowicz Jagiellonian University Medical College, Kraków, Poland
REVIEW RETURNED	17-Sep-2018

GENERAL COMMENTS	The paper presents a study protocol for a phase II cluster randomised controlled trial for the evaluation of feasibility and acceptability of a multicomponent nonpharmacological delirium prevention intervention for inpatients with advanced cancer. Despite delirium being a serious complication for hospitalized patients with advanced cancer, high quality data on delirium prevention is still lacking. Thus, the research questions raised in the present manuscript are very important for palliative research and clinical care. The study is well-designed, and the manuscript is well-written. There are a few minor comments. Q2. Could you please clarify on the sample size? Abstract: “The primary outcome is adherence to the intervention during the first seven days of admission, as measured for 60 consecutively admitted eligible patients.”, Sample size section: “We will collect de-identified data on all eligible patients admitted to all sites until data is collected for 40 patients overall, with at least 20 in the intervention arm. [...]”. Q3. Is there the minimum number of patients planned for each of the participating study sites? Is there a risk of unequal participation of the study sites? Q4. Are there any exclusion criteria from the study? (e.g. Terminal -death is likely within hours, delirium on admission).

	Q4. Methodology- Intervention- lack of information on the methods of: a. Fall risk assessment b. Hearing assessment c. Vision assessment d. Baseline cognition assessment Q4. Substudy- brief interview Could you please be more specific on the course and the aim of the interview? Structured, semi-structured? Q4. “Sustainability of the intervention: Adherence will be measured for all inpatients over one week, six months after commencement of data collection at the intervention sites”- lack of information in the previous sections (e.g. Data collection, Assessment) and in the Study diagram. Q6. How would you calculate adherence to the intervention if implementation section (Table 1) provides from 3 to 7 delirium prevention methods? Successful when used any out of 7 or 7 out of 7 techniques applicable for the particular patient? Q6. “The primary outcome is adherence to the intervention. A rate of at least 60% of patients having at least four completed domains for at least five of the first seven days of admission will be considered minimum evidence that the intervention is feasible without need for major modification of the intervention or its delivery methods”, however “The phase II trial will not pre-determine delivery methods for the intervention..” Could you please clarify how would you check if there is a need to modify the intervention or its delivery methods, if delivery methods will not be pre-determine? Q6. Secondary outcome nb 2: “Fidelity to delirium screening, diagnosis and the intervention: degree of alignment with the protocol, rationales for adaptation, rate of protocol deviations without reasons.” Could you please specify the measures being planned to use? Q6. Secondary outcome nb 3: “Methods, areas and levels of interdisciplinary involvement in delivery of the intervention;” Could you please specify on the levels of interdisciplinary involvement? Q13. Page numbers listed in the SPIRIT Checklist do not cover addressed issues. Additionally, “The delirium prevention intervention will be delivered to all eligible patients from admission until discharge or death by members of the interdisciplinary team and volunteers. “ If a family partnership is included as an additional domain, should not family members/caregivers be listed jointly with the members of the interdisciplinary team and volunteers? Could you please provide the rationale on your special interest in breast cancer patients.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewers
Thank you to each of the three reviewers for the constructive comments on our protocol manuscript. Please find our responses below.
In addition to the changes outlined below, we have added the four objectives of the study to the manuscript (in red, below and on pages 6-7), to more clearly outline the purposes of the study to the reviewers, and future readers.
These are:
1. To develop a multi-component non-pharmacological delirium prevention intervention ('non-pharmacological delirium prevention intervention'), derived from highly efficacious interventions for older adults in hospital, for people with advanced cancer and palliative care inpatient unit settings;
2. To describe the strategies used by participating sites to implement the delirium measurement tools and non-pharmacological delirium prevention intervention;
3. To determine if a non-pharmacological delirium prevention intervention is feasible, acceptable and deliverable with high adherence and fidelity in oncology and palliative care units;
4. To determine the feasibility and design of a phase III trial to test the efficacy of the non-pharmacological delirium prevention intervention in people with advanced cancer in hospital.

Reviewer 1 Tammy Hshieh, Institution and Country: Brigham and Women's Hospital; Dana-Farber Cancer Institute, USA

Reviewer 1: This paper addresses an important and interesting topic in delirium that remains incompletely answered. Specifically, whether patients with advanced cancer would benefit from multicomponent non-pharmacological intervention to prevent delirium. The methodology of these authors in designing and evaluating a clinical program to do so is thoughtful and robust. I look forward to reading about the results of this study, and the subsequent multi-site phase III cluster RCT if this one deems it feasible. I am a bit disappointed that delirium incidence and severity are only secondary outcomes in this current study but understand that adherence is the primary question here. I wonder if delirium incidence and severity should potentially be considered primary outcomes.

Response: Thank you. As a phase 2 trial, the present study was not powered to detect statistically significant differences in delirium incidence and severity, which is why we decided that these were best measured as secondary outcomes. Delirium incidence or severity will be the primary outcome of the phase 3 trial. The value of measuring delirium incidence and severity in the present trial was to: i) determine the feasibility and acceptability of the delirium ascertainment process and measures in this patient population and setting; ii) provide data about the local rate of delirium occurrence, to inform (along with previous epidemiological data) calculation of the sample size for the phase 3 trial; and iii) be the means by which to establish whether there was any signal that the intervention decreased delirium incidence or severity.

Reviewer 1: Previous multicomponent interventions, as discussed by the authors on Page 5 did not show an impact on delirium but the authors are able to clearly explain limitations and issues with that study. If this current ambitious study demonstrates good adherence but no impact on delirium, though, would a Phase III trial necessarily be executed?

Response: Yes. We will proceed with a phase 3 trial if the results and findings of the present study indicate the intervention and study processes are feasible and acceptable, because otherwise the question of whether or not the intervention reduces delirium incidence and/or severity in this patient population and setting will remain unanswered.

Reviewer 1: Finally, I definitely see the merits of multicomponent delirium intervention in advanced cancer patients but the authors raise the concern that others may not appreciate this study on page 8 ("delirium may be considered innocuous in advanced cancer and palliative care contexts ... preventing delirium is not possible, necessary or likely to be effective.") But the authors to not address why they disagree. It would strengthen the introduction for the authors to address these limitations (of perception by others) directly.

Response: Thank you, an excellent suggestion. We have now added the following sentence (in red) to the relevant section on pages 5-6, as follows:

“There are possible barriers to implementation of non-pharmacological delirium prevention strategies for people with advanced cancer. These include their common frailty and fatigue which reduces capacity to participate in activities such as exercise. Patients and family may not realise the serious risks associated with an episode of delirium, or prioritise prevention strategies without this knowledge. Some clinicians may perceive that delirium is inevitable and innocuous in advanced cancer and palliative care contexts;19,20 and presume that preventing delirium is not possible, necessary or likely to be effective. Clinicians historically have relied on pharmacological intervention for delirium, rather than intentionally striving to prevent delirium through non-pharmacological means. With competing demands and without evidence of effectiveness, hospital managers may not value the importance of preventing delirium or allocate the required resources or personnel for non-pharmacological strategies, particularly for people approaching the end of their life.
Yet, to fulfil the remit of palliative care to help patients live as actively as possible, the adversity of delirium impels further empirical testing to definitively determine whether it can be prevented during advanced cancer. Based on the body of research conducted with older people in hospital described above, 9,14 we hypothesised that a similar multicomponent intervention would reduce delirium incidence and/or decrease its duration and severity in this patient population. Given the noted possible barriers to implementation, piloting the intervention and study design was required prior to testing the hypothesis in a phase III (efficacy) trial.”
Reviewer 2 Asao Ogawa, National Cancer Center Hospital East, Japan

Reviewer 2: Dear authors, Thank you very much for this interesting and exciting work I was able to review. For the better understanding of your study, I have some questions:

1. A multicomponent non-pharmacological intervention is important for preventing delirium in people with advanced cancer. In general strategies for preventing delirium in general hospitals, the interventions involves careful pain control, and avoiding polypharmacy. Maybe it would be better to add the discussion of selecting 5 components.

Response: We agree that optimal pain management and avoidance of polypharmacy are likely to be important in reducing the risk of delirium in hospitalised patients. However, there is less evidence that this component of care is effective in preventing delirium, compared to those which address fundamental human needs for movement, cognition, sleep, hydration, vision and hearing. For example, our team recently submitted for publication a systematic review of non-pharmacological interventions for delirium focused on relevance to patients with life-threatening illness; of the 29 included studies, only seven (i.e. less than one quarter) included a pharmacological component, such as medication reviews and alerts and/or protocols for pain and sedation. We intentionally chose the intervention components of the phase 2 trial because previous reviews (Hshieh et al 2015; Siqqiqi et al 2016) had identified these as being the most commonly present in effective interventions. We have now more explicitly justified our decision not to include a pharmacological component to the intervention by adding the following text (in red) to the relevant paragraph on pages 8-9, as follows:

“The multicomponent delirium prevention intervention involves five domains of care that, when delivered in combination, significantly reduced delirium incidence in older hospitalised patients in previous clinical trials. We added family partnership as an additional domain, as it was recommended by our consumer investigators and an expert working group, is highly valued by patients and family members, and identified as essential by the Australian Commission for Safety and Quality in Healthcare (ACSQHC) in a new Delirium Standard, if preferred by the patient. We did not include a pharmacological component (such as minimising polypharmacy) because there was less evidence that this component of care effectively prevents delirium, compared to that which addresses fundamental human needs for physical and cognitive activity, sleep, hydration, vision and hearing.”

Reviewer 2:

2. In the people with advanced cancer, the factors promoting delirium vary a great deal and some factors are out of control. From the perspective of practice, the data of psychoactive medication and opioids is informative to assessing the behavioral modification of the clinical teams.

Response: Yes, we agree that measurement of psychoactive medication use/dosage is one useful measure of clinical practice change in delirium studies. We considered this to be outside of the scope of the phase 2 trial, but are considering it as an outcome measure in the phase 3 trial.

Reviewer 3 Karolina Piotrowicz, Jagiellonian University Medical College, Kraków, Poland

The paper presents a study protocol for a phase II cluster randomised controlled trial for the evaluation of feasibility and acceptability of a multicomponent nonpharmacological delirium prevention intervention for inpatients with advanced cancer. Despite delirium being a serious complication for hospitalized patients with advanced cancer, high quality data on delirium prevention is still lacking. Thus, the research questions raised in the present manuscript are very important for palliative research and clinical care. The study is well-designed, and the manuscript is well-written. There are a few minor comments.

Reviewer 3: Could you please clarify on the sample size? Abstract: “The primary outcome is adherence to the intervention during the first seven days of admission, as measured for 40 consecutively admitted eligible patients.”, Sample size section: “We will collect de-identified data on all eligible patients admitted to all sites until data is collected for 40 patients overall, with at least 20 in the intervention arm. [...]”.

Response: Thank you for pointing out this discrepancy. We have corrected the number in the abstract. Data collection for 60 patients is correct; however, there will be data pertaining to adherence to the intervention only for 40 patients: i.e. 20 in the first two intervention sites, and then for 20 patients when the two waitlist control sites implement the intervention.

Please note, the whole sample size section does account for the planned data collection for 60 patients:

“A sample size of four sites and 40 patient participants (10 from each site) was considered sufficient for reasonable estimation of feasibility and percentage completion of study processes and measures during the first phase. 40 We will collect de-identified data on all eligible patients admitted to all sites until data is collected for 40 patients overall, with at least 20 in the intervention arm. If the intervention is found to need modification, data will be collected for a further 20 patient participants at the two waitlist control sites.” (bolded emphasis added)
Reviewer 3: Is there the minimum number of patients planned for each of the participating study sites? Is there a risk of unequal participation of the study sites?

Response: The planned number of patients from each of the four sites is 10, so there will not be the risk of unequal participation of the study sites. We have made this clearer in the manuscript by adding the following text to the relevant section of page 19 (in red):

“A sample size of four sites and 40 patient participants (10 from each site) was considered sufficient for reasonable estimation of feasibility and percentage completion of study processes and measures during the first phase.”

Reviewer 3: Are there any exclusion criteria from the study? (e.g. Terminal -death is likely within hours, delirium on admission).

Additionally, “The delirium prevention intervention will be delivered to all eligible patients from admission until discharge or death by members of the interdisciplinary team and volunteers. “ If a family partnership is included as an additional domain, should not family members/caregivers be listed jointly with the members of the interdisciplinary team and volunteers?

Combined response to both comments: No patients were excluded from data collection in the main study, as we sought to determine the feasibility and acceptability of the intervention for all adult patients with advanced cancer in these palliative care settings, including those in the terminal phase and those with delirium. The inclusion of all eligible patients is provided in paragraph 3 of page 8. Please note, here we have made two adjustments to the text, one in response to your suggestion to acknowledge the involvement of family, and the second to more correctly represent the time frame for data collection, from:

“The delirium prevention intervention will be delivered to all eligible patients from admission until discharge or death by members of the interdisciplinary team and volunteers”

to:

“The delirium prevention intervention will be delivered to all eligible patients for the first seven days of admission by members of the interdisciplinary team, family caregivers and volunteers.”

Reviewer 3: Methodology- Intervention- lack of information on the methods of:

a. Fall risk assessment
b. Hearing assessment
c. Vision assessment
d. Baseline cognition assessment

Response: As stated on page 11, we did not pre-determine delivery methods for the intervention in this phase 2 trial. Instead, we observed the delivery methods of each site, in order to learn from the site teams about their established practice, as well as what practices they needed to establish. (page 12) For example, all sites are mandated by Australian hospital accreditation standards to assess every patient’s risk of falls at and during admission, so this assessment was pre-existing. Whereas, in the course of conducting the trial, it appears that processes for hearing, vision and baseline cognition assessment may need to be established by the site teams. These important learnings will be reported in a planned publication about the implementation of the study intervention.

Reviewer 3: Substudy - brief interview - Could you please be more specific on the course and the aim of the interview? Structured, semi-structured?

Response: Thank you. We have added the following text (in red) to provide more detail about the method and purpose of the interviews to page 17, as follows:
“A qualitative sub-study will be conducted to obtain patient, family caregiver, staff and volunteer perceptions of the feasibility and acceptability of the intervention strategies (e.g. receiving information from staff about delirium) and study measures via brief, semi-structured interviews.”

Reviewer 3: “Sustainability of the intervention: Adherence will be measured for all inpatients over one week, six months after commencement of data collection at the intervention sites”- lack of information in the previous sections (e.g. Data collection, Assessment) and in the Study diagram.

Response: Thank you again! We have corrected this oversight by additions to the study diagram and adding the following text (in red) to page 13:

“At study completion, the project team will collect PCOC data for the study time-frame (Age, Gender, Country of birth, Preferred language, Aboriginal or Torres Strait Islander status, Primary diagnosis, Length of stay, Performance status [Australian-modified Karnofsky Performance Status (AKPS)30 and Resource Utilisation Groups - Activities of Daily Living (RUG-ADL)],31 Palliative care phase). 32 For the sustainability outcome, site research nurses will collect intervention adherence data at six months for all inpatients for one week.”

Reviewer 3: How would you calculate adherence to the intervention if implementation section (Table 1) provides from 3 to 7 delirium prevention methods? Successful when used any out of 7 or 7 out of 7 techniques applicable for the particular patient?

Response: We will report both the adherence to each strategy (i.e. 7 out of 7), and adherence to care within each domain (i.e. any out of 7).

Reviewer 3: “The primary outcome is adherence to the intervention. A rate of at least 60% of patients having at least four completed domains for at least five of the first seven days of admission will be considered minimum evidence that the intervention is feasible without need for major modification of the intervention or its delivery methods”, however “The phase II trial will not pre-determine delivery methods for the intervention..” Could you please clarify how would you check if there is a need to modify the intervention or its delivery methods, if delivery methods will not be pre-determine?

Response: We will determine if there is a need to modify the intervention or its delivery methods of adherence to the intervention is lower than the pre-specified rate of 60%, as outlined in the section on the study endpoints (page 18). Delivery methods are being observed through collaboration with the site investigators, research nurses, working groups and interview data from patients, family caregivers, staff and volunteers.

Reviewer 3: Secondary outcome nb 2: “Fidelity to delirium screening, diagnosis and the intervention: degree of alignment with the protocol, rationales for adaptation, rate of protocol deviations without reasons.” Could you please specify the measures being planned to use?

Response: Thank you. We will measure these outcomes via case report forms, which has now been specified in the manuscript (and for other outcomes where relevant (pages 18-19).

Reviewer 3: Secondary outcome nb 3: “Methods, areas and levels of interdisciplinary involvement in delivery of the intervention;” Could you please specify on the levels of interdisciplinary involvement?

Response: We will report the level of interdisciplinary involvement by describing which discipline was involved in delivering each strategy and proportionally for each domain. For example, of the team,

nurses delivered x% of the strategies within the sleep domain. This will be possible through data collection on the specially designed checklist, as outlined on page 14:
“At intervention sites, specially designed checklists will capture family caregivers, staff and volunteers’ delivery (or otherwise) of delirium prevention strategies within each domain of the multicomponent intervention (Table 1), as well as who delivered it. From this, we will determine the level of involvement of family caregivers, interdisciplinary staff, and volunteers for each strategy.”

Reviewer 3: Page numbers listed in the SPIRIT Checklist do not cover addressed issues.

Response: Thank you, we have corrected the page numbers.

Reviewer 3: Could you please provide the rationale on your special interest in breast cancer patients.

Response: The study was funded by the National Breast Cancer Foundation. The funder did not specify that only patients with breast cancer be studied, but in view of the source of funding, we decided to focus some attention on this small patient sub-group, where possible. We have added the following text (page 19):

7. Number of people with advanced breast cancer admitted to the units, number of these who are in underserved populations (patients over 70, indigenous patients, and culturally and linguistically diverse backgrounds), and the number who experience an episode of delirium (total, and in under-served populations) (for the purposes of reporting to the trial funder, the National Breast Cancer Foundation);

Editor: We have noticed that you have uploaded the file "Letter - REO - HE17122 - Approval - Ethics", "Letter - REO - HE17 122 - Approval - Amendment 1-signed" and "Outcome letter Fax Back Form_PS-17-030 - Meera Agar" under 'supplementary file'. However, we can't see any citation for this file within the main text. If this file needs to be published as supplementary file, please cite it as 'supplementary file' in the main text and upload it in PDF format. Otherwise, you can email us confirming that this file is for 'for review only'.

Response: Apologies for the confusion. The documents related to ethical approval of the study are for the editor’s review only.

Editor: We have implemented an additional requirement to all articles to include 'Patient and Public Involvement’ statement within the main text of your main document. Authors must include a statement in the methods section of the manuscript under the sub-heading 'Patient and Public Involvement'. This should provide a brief response to the following questions:

Editor: How was the development of the research question and outcome measures informed by patients’ priorities, experience, and preferences?

Response: The research question and study rationale and processes were informed by the literature pertaining to patients’ experiences of delirium, as briefly outlined in the introduction (page 4). There is now extensive literature that delirium is highly distressing and deleterious to patients.

“During delirium, feelings of fear, humiliation, confusion and isolation are common, 4 at a time when connection with family, friends and health professionals is important and highly valued. 5 Family experience high levels of distress as a result.5 Delirium is further associated with increased falls, pressure areas, longer-term cognitive and functional decline, duration of hospital stay, mortality, and health care costs.6-8

References:
4. O'Malley G, Leonard M, Meagher D, O'Keeffe ST. The delirium experience: a review. Journal of Psychsomatic Research. 2008;65(3):223-228.
5. Finucane AM, Lugton J, Kennedy C, Spiller JA. The experiences of caregivers of patients with delirium, and their role in its management in palliative care settings: an integrative literature review. Psycho-Oncology. 2017;26(3):291-300.
6. National Institute for Health and Clinical Excellence (NICE) National Clinical Guideline centre. Delirium: diagnosis, prevention and management. 2010; http://www.nice.org.uk/nicemedia/live/13060/49908/49908.pdf. Accessed July 13th, 2011.
7. Australian Commission on Safety and Quality in Health Care. Evidence for the safety and care of patients with a cognitive impairment in acute care settings: a rapid review. In. Sydney: ACSQHC; 2013.

Low-burden outcome measures (e.g. the Nursing Delirium Screening Scale) were deliberately chosen in order to minimise the impact of the study on patients with advanced illness.

Editor: How did you involve patients in the design of this study?

Response: No patients were involved in the design of the study. Two family caregiver consumers are involved in the study as associate investigators (co-authors M. Brassil and B. Noble).

Editor: Were patients involved in the recruitment to and conduct of the study?

Response: No.

Editor: How will the results be disseminated to study participants?

Response: It is unlikely that patients and family caregivers who participated in the study will receive feedback about the study, as the coordinating centre does not have access to the names or contact information for these study participants. A written and verbal report of the study results and findings will be provided to the participating sites.

Editor: For randomised controlled trials, was the burden of the intervention assessed by patients themselves?

Response: We are seeking to include the perspectives of patients about the feasibility and acceptability of the intervention through brief semi-structured interviews (see page 17).

Editor: Patient advisers should also be thanked in the contributorship statement/acknowledgements. If patients and or public were not involved please state this.

Response: Agree. We plan to thank patient, family caregiver, staff and volunteer participants in the publication of the study results.

VERSION 2 – REVIEW

REVIEWER	Tammy Hshieh Brigham and Women's Hospital, United States
REVIEW RETURNED	24-Oct-2018

GENERAL COMMENTS	Page 45 - Line 14. The sentence that was added is a bit awkward: "Yet, to fulfil the remit of palliative care to help patients live as actively as possible, the adversity of delirium impels further empirical testing to definitively determine whether it can be prevented during advanced cancer." I would change it to say: Delirium makes it difficult for patient in palliative care to accomplish the goal of still living as actively as possible. Thus, it is important to study this question of whether delirium can be prevented during advanced cancer." I do like the new, clearly stated objectives. Assessing for sustainability is important, so it is good the authors have added the 6 months post intervention review of whether interventions were still in practice.

REVIEWER	Asao Ogawa National Cancer Center Hospital East, Japan
REVIEW RETURNED	06-Nov-2018

GENERAL COMMENTS	Dear authors, Thank you very much for this excellent work i was able to review. The authors responded appropriately to the comments. I hope this trial will be successful.

REVIEWER	Karolina Piotrowicz MD, PhD Jagiellonian University Medical College, Kraków, Poland
REVIEW RETURNED	21-Oct-2018

GENERAL COMMENTS	Accepted after a revision.

VERSION 2 – AUTHOR RESPONSE

Dear Ms Howard and Ms Johnson, thank you for the accept decision and to the reviewers for their time spent and supportive comments. In response, the highlighted sentence has been changed to: "Despite these barriers, the remit of palliative care to help patients live as actively as possible makes it important to study whether delirium can be prevented during advanced cancer." I have also taken the opportunity to make a few very small edits, as per the marked copy.