PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Outpatient Palliative Care Referral System (PCRS) for patients with advanced cancer. An impact evaluation protocol.
AUTHORS	Brunelli, Cinzia; Zecca, Ernesto; Pigni, Alessandra; Bracchi, Paola; Caputo, Mariangela; Lo Dico, Silvia; Fusetti, Viviana; Tallarita, Antonino; Bergamini, Cristiana; Brambilla, Marta; Raimondi, Alessandra; Niger, Monica; Provenzano, Salvatore; Sepe, Pierangela; Alfieri, Sara; Tinè, Gabriele; De Braud, Filippo; Caraceni, A

VERSION 1 – REVIEW

REVIEWER	Trygve Johannes Lereim Sævareid University of Oslo
REVIEW RETURNED	18-Feb-2022

GENERAL COMMENTS	Dear authors Congratulations on your submission. It is a well-written and well-organized article. Abstract: Overall, a clear and informative abstract. However, I find that the "Intervention" section describes the design and that the PCRS is the intervention. Should it be mentioned in the abstract something like "this is the protocol of …"? Strengths and limitations: The first bullet point merely informs of the aims of the study, it does not specify anything about strengths and limitations. Please specify whether what is written is a strength or a limitation. Main text - Many abbreviations. Please consider reducing the number. For example, the American Society of Clinical Oncology (ASCO) – ASCO is written only once, and it is probably not necessary to include the abbreviation ASCO in the text. - A nice introduction leading up to the aims of the project - Page 7, lines 13-15: Please consider removing "Study outcomes will be patient's satisfaction with care, quality of life, caregiver's satisfaction with care and use of health care resources." because it is also mentioned in the Methods section (which is the more appropriate section, in my opinion). - Page 7, line 29: "with standardized validated patient reported outcome measurements". It is unclear to me what this means. Is it "knowledge-based instruments" or something similar? - Nice presentation of the NGT - Methods o The authors state that the PCRS intervention will be implemented. In the aims it is written that the project will "evaluate the impact of

	routine application". In the discussion the project is presented as an implementation study. Because of that could the authors should write something about how they will implement the PCRS. - Discussion. Please consider to add headlines to increase reader friendliness. Best of luck!

REVIEWER	Carlos Paiva Barretos Cancer Hospital, Department of Clinical Oncology
REVIEW RETURNED	14-Mar-2022

GENERAL COMMENTS	I would like to congratulate the authors for choosing such a relevant topic! Although the recommendations to integrate palliative care within 8 weeks of diagnosis are well accepted, I agree with the authors that it is a very superficial recommendation. What is "early" for a luminal breast cancer patient with bone-only meastasis is completely distinct from what is early for a patient with esophageal or pancreatic metastatic cancer, for example. So I think this study is very well justified. The choice of method seemed well justified to me, because a randomized clinical trial would have the "contamination" bias really. Also, a cluster randomized trial, would have the technical difficulty of the number of clinical units to be randomized. I have some doubts about the statistical analysis planned: 1. Why compare baseline to mean of the other outcome measures and not specifically to a time point (e.g. time point 3). I believe that, as a primary objective, comparing baseline satisfaction scores with time point 3 (90 days) would be very pertinent. The comparisons between baseline and mean of subsequent measures could be a secondary outcome. 2. Another question: why was an effect size of 0.32 set? Based on what? 3. Was the number of patient losses considered in the sample size estimation? In general, studies of palliative care patients are associated with attrition rate of ~20-30%.

REVIEWER	Soumya Niranjan The University of Alabama at Birmingham School of Health Professions, Health Services Administration
REVIEW RETURNED	21-Mar-2022

GENERAL COMMENTS	This is an important study and its well written

REVIEWER	Eric C.T. Geijteman Erasmus University Medical Centre, Medical Oncology
REVIEW RETURNED	21-Mar-2022

GENERAL COMMENTS	Thank you for the opportunity to review this work. The manuscript is well-written and understandable. Therefore, I have no major comments on the manuscript. I have two minor questions: 1. where is Table 1 (p. 5, line 43)? 2. in Figure 1 the project scheme is presented. It highlights that NGT on PCRS appropriateness and applicablity is followed by pilot testing and then adjustments of PCRs and of implementation strategies are

	made. However, in the text (p. 6, line 4 to 10) it is stated that 'based on the NGT results, the PCRs will be adjusted/modified as needed and standard implementation procedures will be developed. Then a pilot cross-sectional...'.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Dr. Trygve Johannes Lereim Sævareid, University of Oslo Comments to the Author:

Dear authors
Congratulations on your submission. It is a well-written and well-organized article.

Abstract:

1. Overall, a clear and informative abstract. However, I find that the "Intervention" section describes the design and that the PCRS is the intervention. Should it be mentioned in the abstract something like "this is the protocol of …"?

   We agree with the reviewer. In the abstract the Intervention section now reads: "Implementation of PCRS for the identification of advancer cancer patients in need of palliative care in routine outpatient cancer care".

2. Strengths and limitations: The first bullet point merely informs of the aims of the study, it does not specify anything about strengths and limitations. Please specify whether what is written is a strength or a limitation.

   The sentence has been changed as follows :
   "The development and implementation of a palliative care reference system (PCRS) that takes into account published evidence and consensus among oncology and palliative care professionals constitute a strength of this project".

Main text

3. Many abbreviations. Please consider reducing the number. For example, the American Society of Clinical Oncology (ASCO) – ASCO is written only once, and it is probably not necessary to include the abbreviation ASCO in the text.
   Thank you. We have removed the unnecessary abbreviations (ASCO – HCPs – EPC)
4. A nice introduction leading up to the aims of the project
5. Page 7, lines 13-15: Please consider removing "Study outcomes will be patient's satisfaction with care, quality of life, caregiver's satisfaction with care and use of health care resources." because it is also mentioned in the Methods section (which is the more appropriate section, in my opinion).
   OK. We have removed it
6. Page 7, line 29: "with standardized validated patient reported outcome measurements". It is unclear to me what this means. Is it "knowledge-based instruments" or something similar?
   We changed the wording into :
   "validated self reported questionnaires" and added the following quotation :
   US Department of Health and Human Services FDA Center for Drug Evaluation and Research, US Department of Health and Human Services FDA Center for Biologics Evaluation and Research, US Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes. 2006;4:1–20
7. Nice presentation of the NGT

Methods

8. The authors state that the PCRS intervention will be implemented. In the aims it is written that the project will “evaluate the impact of routine application”. In the discussion the project is presented as an implementation study. Because of that could the authors should write something about how they will implement the PCRS.
   We agree with the reviewer. The following paragraph was added to the method section:
   PCRS implementation
   For implementing the PCRS, patient clinical assessment will be performed initially by a nurse, collecting self reported questionnaires and partially completing the PCRS. This evaluation will be entered in the electronic medical records and then integrated and validated by the oncologist during the visit. The oncologist will finally decide to refer or not the patient to PC using the PCRS predefined criteria and his or her clinical judgement.
9. Discussion. Please consider to add headlines to increase reader friendliness.
   We have structured the paragraph with headlines
   Discussion
   Different early palliative care models
   Palliative care needs selection criteria
   The PCRS project

Best of luck!

Reviewer 2

Dr. Carlos Paiva, Barretos Cancer Hospital Comments to the Author:
I would like to congratulate the authors for choosing such a relevant topic!

Although the recommendations to integrate palliative care within 8 weeks of diagnosis are well accepted, I agree with the authors that it is a very superficial recommendation. What is “early” for a luminal breast cancer patient with bone-only meastasis is completely distinct from what is early for a patient with esophageal or pancreatic metastatic cancer, for example. So I think this study is very well justified.
The choice of method seemed well justified to me, because a randomized clinical trial would have the “contamination” bias really. Also, a cluster randomized trial, would have the technical difficulty of the number of clinical units to be randomized.

I have some doubts about the statistical analysis planned:

1) Why compare baseline to mean of the other outcome measures and not specifically to a time point (e.g. time point 3). I believe that, as a primary objective, comparing baseline satisfaction scores with time point 3 (90 days) would be very pertinent. The comparisons between baseline and mean of subsequent measures could be a secondary outcome.
   The definition of the main study outcome was extensively discussed by the research team. The choice was motivated by the need to compare the two groups considering a wider period of time rather than just one time point, both from a clinical point of view and also because this is expected to be a more reliable estimate of the outcome (multiple measurements increase reliability). In addition, averaging on multiple non missing follow-up assessments allows to include in the analysis also those patients with missing data on a single predefined assessment (i.e. day90) but non missing in the others.

2) Another question: why was an effect size of 0.32 set? Based on what?

Sample size determination is an important and often difficult step in planning an empirical study. From a statistical perspective, sample size depends on the type of analysis to be performed, the desired power and type I error of the statistical tests performed, the minimum detectable effect size. However also feasibility issues (practical limitations on access to a population of interest as well as he availability of time and resources) play a relevant role. In planning this study we started from feasibility issues and estimated that 150 patients in each phase could be enrolled in the time and with the resources planned. Then, given the overall 300 patients sample size, we calculated the minimum detectable effect size (0.32 in the original text) based on a 90% power and a 5% alpha error.
Relevant to note is also that in revising calculations we found a typo: the minimum detectable effect size for 300 pts with a 90% power is actually 0.37 and not 0.32. (0.32 was the effect size for a power of 80%, N=300). The typo was corrected in the text.
We hope this clarifies the decision process about sample size determination.

3) Was the number of patient losses considered in the sample size estimation? In general, studies of palliative care patients are associated with attrition rate of ~20-30%.
We agree with the reviewer that the potential attrition needs to be addressed. Despite advanced, the target population of this study is not in the end of life phase and a number of them will not be in need of palliative care, so we estimate a 15% attrition rate. We then estimated the loss of power (from 90% to 85%) in case of a 15% attrition rate and reported it in the power paragraph:
"In case of a 15% attrition rate the study power diminishes at 85%, all else unchanged"

Reviewer 3
Dr. Soumya Niranjan, The University of Alabama at Birmingham School of Health Professions
Comments to the Author:
This is an important study and its well written
We are grateful to reviewer 3 for the appreciation of our work

Reviewer 4
Dr. Eric C.T. Geijteman, Erasmus University Medical Centre Comments to the Author:
Thank you for the opportunity to review this work. The manuscript is well-written and understandable. Therefore, I have no major comments on the manuscript. I have two minor questions:

1) where is Table 1 (p. 5, line 43)?
Table 1 is placed just before "Power consideration and statistical analysis"

2) in Figure 1 the project scheme is presented. It highlights that NGT on PCRS appropriateness and applicability is followed by pilot testing and then adjustments of PCRs and of implementation strategies are made. However, in the text (p. 6, line 4 to 10) it is stated that 'based on the NGT results, the PCRs will be adjusted/modified as needed and standard implementation procedures will be developed. Then a pilot cross-sectional...'.
It is right that figure 1 shows a final step after the pilot testing but this is also reported consistenly at the end of the paragraph partially mentioned by the reviewer which indeed reads:
"A final revision of the PCRS and of its implementation procedure by the study group will follow the pilot testing".

VERSION 2 – REVIEW

REVIEWER	Carlos Paiva Barretos Cancer Hospital, Department of Clinical Oncology
REVIEW RETURNED	24-Jul-2022

GENERAL COMMENTS	Thank you for the opportunity to read this very interesting protocol again. The key point of the idea, in my opinion, is the completion by the nurse. Another option would be to provide automatic triggers for physicians to remember to fill out the protocol in specific situations (starting a new palliative chemotherapy, staging IV, etc). I have only two small comments (suggestions) for the authors: 1. I suggest including the Earle CC et al. criteria (PMID: 18688053) among the end-of-life assessments in patients who die to systematize the assessment process: "Proportion receiving chemotherapy in the last 14 days of life"; "Proportion with > 1 ER visit in the last 30 days of life"; "Proportion with > 1 hospitalization in the last 30 days of life"; "Proportion admitted to the ICU in the last 30 days of life"; "Proportion dying in an acute care setting"; "Proportion not admitted to hospice"; "Proportion admitted to hospice for less than 3 days". Thus, as done by other authors, it is possible to include an Aggressiveness of Care Score using the Earle et al. criteria. 2. As cited by the authors, David Hui et al by means of Delphi created a set of palliative care referral indicators. Other authors, based on this study, have created a referral tool. Please, consider including the reference below, in the discussion, at the end of the 8th paragraph: Paiva CE, Paiva BSR, Menezes D, Zanini LE, Ciorlia JB, Miwa MU, Hui D. Development of a screening tool to improve the referral of patients with breast and gynecological cancer to outpatient palliative care. Gynecol Oncol. 2020 Jul;158(1):153-157. doi: 10.1016/j.ygyno.2020.04.701. Epub 2020 Apr 30. PMID: 32362569.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2

Dr. Carlos Paiva, Barretos Cancer Hospital

Comments to the Author:

Thank you for the opportunity to read this very interesting protocol again. The key point of the idea, in my opinion, is the completion by the nurse. Another option would be to provide automatic triggers for physicians to remember to fill out the protocol in specific situations (starting a new palliative chemotherapy, staging IV, etc).

R. Thank you for your comment. Regarding triggers for physicians, we planned to introduce the new PCRS tool in the electronic medical record, which clinicians consult at each visit. Despite not being a formal reminder, this modality should facilitate the task of clinicians in PC needs assessment. (Please see Phase II: PCRS implementation and impact evaluation: "*This evaluation will be entered in the electronic medical records and then integrated and validated by the oncologist during the visit*")

I have only two small comments (suggestions) for the authors:

1. I suggest including the Earle CC et al. criteria (PMID: 18688053) among the end-of-life assessments in patients who die to systematize the assessment process: "Proportion receiving chemotherapy in the last 14 days of life"; "Proportion with > 1 ER visit in the last 30 days of life"; "Proportion with > 1 hospitalization in the last 30 days of life"; "Proportion admitted to the ICU in the last 30 days of life"; "Proportion dying in an acute care setting"; "Proportion not admitted to hospice"; "Proportion admitted to hospice for less than 3 days". Thus, as done by other authors, it is possible to include an Aggressiveness of Care Score using the Earle et al. criteria.

R1. We agree with the reviewer on the importance of collecting this information. Since the study has already started enrolling patients, we are collecting most of the data that are now more specifically listed in the amended manuscript. We also added the Earle et al. quotation.

"For those patients who will die during the follow-up period, a dedicated research nurse will collect the following data relative to the last 30 days of life: active oncological treatments administration (chemotherapy, radiotherapy, immunotherapy, etc.) and date of last administration, number of ER visits, hospitalization (number and length in days), activation of any PC service (home care or hospice) and place of death. The above information will allow us to calculate end-of-life care quality indicators, like the proportions of patients with chemotherapy in the last 14 days of life [3]".

2. As cited by the authors, David Hui et al by means of Delphi created a set of palliative care referral indicators. Other authors, based on this study, have created a referral tool. Please, consider including the reference below, in the discussion, at the end of the 8th paragraph:
Paiva CE, Paiva BSR, Menezes D, Zanini LE, Ciorlia JB, Miwa MU, Hui D. Development of a screening tool to improve the referral of patients with breast and gynecological cancer to outpatient palliative care. Gynecol Oncol. 2020 Jul;158(1):153-157. doi: 10.1016/j.ygyno.2020.04.701. Epub 2020 Apr 30. PMID: 32362569.

R2. We recognize the importance of the study to which the reviewer refers and have therefore cited it (ref 51) among the studies specifically designed to improve the appropriate selection of cancer patients for referral to outpatient specialized palliative care. We added a sentence including data from Paiva et al. results.

"In the study by Paiva et al., the use of the PC referral tool would have increased referral rate by 3.2 fold [51]."