## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | A longitudinal study of symptom burden in outpatients with advanced cancers based on Electronic Patient Reported Outcome (ePRO) platform: a single institution, prospective study protocol |
| **AUTHORS** | Tang, Lili; Pang, Ying; He, Yi; Shi, Qiuling; Han, Xinkun; Li, Zimeng; Zhou, Chengcheng; Zhou, Yuhe; He, Shuangzhi; Wang, Yan; Zhang, Yening; Song, Lili; Wang, Bingmei; Li, Xiumin |

## VERSION 1 - REVIEW

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| **REVIEWER** | Christina Baggott<br>Medical Research Institute of New Zealand |
| **REVIEW RETURNED** | 17-Mar-2020 |

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| **GENERAL COMMENTS** | Overview<br>This manuscript describes a protocol for an observational study investigating use of an electronic patient reported outcome platform into care of oncology patients in China. The intention is that such a system would allow improved symptom management. Overall I feel this study describes an innovative intervention that could benefit oncology patients by improving symptom management and leading to better care and outcomes.<br><br>Major comments<br>I appreciate that writing in a language which is not your first language is difficult, however, in places incorrect use of tense, prepositions or adverbs etc. makes the meaning of some sentences more difficult to understand.<br><br>Please could the authors clarify if this is a feasibility study to investigate the use of an electronic patient recorded outcome platform or was this data being used to change management and in what way? Was it integrated into patient records and would it be reviewed at the next clinic appointment or would worsening symptoms as captured by the ePRO prompt a more urgent review or a change in management or medication?<br><br>The authors have mentioned there will be a qualitative component to understand why symptoms are not improving but they have not provided any details on the qualitative methodology. Please can they provide this information. For example would they use face to face interviews or focus groups, or will they be done over the phone? What is the analysis framework that will be used to analyse the qualitative data, will there be an interview guide and how was this developed? |

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| | Minor comments<br>Abstract:<br>Please could you make the description of the primary outcome measure more explicit as I am not clear on what the authors mean by “the study of symptom burden”. Is the primary outcome to test the feasibility of collecting this data or is it to look for changes in symptom burden?<br>Secondary outcomes – I am not clear what the authors mean by “reasons of no changes of symptom burden”. Are the authors expecting symptoms to be improving or getting worse? Are they just interested in patients whose symptoms are stable and not changing?<br><br>Strengths and limitations bullet points:<br>I am unclear if the study was 4 weeks long with follow up once a week how there would be 7 follow up episodes.<br><br>Introduction:<br>Page 9 the authors have commented that email is not widely used by the elderly in China, please could they clarify if is Wechat is used by this population? I am not sure that it is accurate to say in Western culture electronic application is mainly through email.<br>Page 9 I appreciate there are cultural differences between Chinese and Western culture, however, I think that the intervention that this study describes could be replicated in many countries allowing for the use of alternative mobile platforms, and the results would be widely applicable. I think this is a strength of this study which the authors may want to discuss.<br><br>Methods<br>Page 10 please clarify how are patients self-referred, was this through advertising or word of mouth?<br>Page 10 more details on the inclusion and exclusion criteria are needed. For example please clarify if the patients are undergoing active treatment for cancer or palliative symptomatic management or a combination of both. This would help the reader understand who the patient population is.<br>Page 11 following primary objective I think pain has been missed from the list of target symptoms being monitored as it is present in the abstract.<br>Page 12 what scoring scale was being used to measure pain and nausea and vomiting? Was this MDASI? Would a table listing the outcome measures and the symptoms they are measuring be clearer?<br>Page 12 please could the authors clarify what is meant by “the percentage of patients who met the eligibility criteria agreed to participate in the study is 80%”<br>Page 13 outcome 3 the authors say semi-structured interviews will be conducted in patients whose symptom score improvement is less than 2, which scale dose this refer to and what about patients whose symptom scores worsen?<br>Page 13 please can the authors provide details on how the 5 additional items for specific cancer sites were selected, and what was the rationale for choosing these symptoms. For example I am unclear why constipation is specific to lung cancer but not other cancer sites?<br>Page 15 following the description of the ePRO platform it would aim the reader to see some screen shots of how the platform looked to patients and if possible provide an English translation.<br>Page 15 please provide information on how the information from the |

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| | ePRO platform was integrated into the patients' care. Was it merged with the patients' hospital records? Did the data lead to a change in management? Did the patients receive earlier review or input from for example palliative care or pain specialists if they reported worsening pain? |

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| **REVIEWER** | Victor Chang<br>VA New Jersey Health Care System<br>East Orange, NJ<br>USA |
| **REVIEW RETURNED** | 11-Apr-2020 |

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| **GENERAL COMMENTS** | This is an interesting and important protocol. The authors need to pay more attention to details.<br><br>Major points<br>Primary purpose of the study is different in different parts of the protocol. Is it to measure symptom burden, or changes in symptom burden?<br>Purposes of the study in the abstract, and in the introduction, and in the methods, are different for the secondary goals. Should be the same. In the introduction, secondary goals include "We also aim to examine the experience, acceptance and compliance of patients with the ePRO platform." In the methods and analysis, secondary goals are "feasibility of using ePRO, symptom related QoL, reasons for no changes of symptom burden, defining frequency of PRO assessments and cut-points, items for screening, and management of comorbidity." Under study objectives, secondary goal #7 is Analyzing the effects of co-morbidity and chronic diseases on symptom burden and symptom management of cancer patients.<br><br>Conclusion of the abstract - This study will provide a rational synthesis of current methods and evidences for using ePRO in psycho-oncology outpatient clinic – this type of conclusion is the result of a review paper.<br><br>Strengths and limitations - A relatively small sample size may be a limitation. – It is not a limitation if the sample size is properly calculated.<br><br>Under data analysis, "the transcription of qualitative interview will be coded and analyzed using NVivo 11.0." but a qualitative interview is mentioned only under study objectives #3 and then outcomes #3. The authors need a methodology paragraph where the 7 followups of the research subject are listed. This interview must be one of the followups<br><br>There is no mention of how study subjects will be recruited, and consented.<br><br>The authors identify target symptoms and different symptom instruments. Which instruments will be used to assess the target symptoms?<br><br>There is no mention of how management of symptoms will be tabulated or analyzed. The only statement is that weChat can capture this information |

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| | Minor points<br>Strengths and limitations - The study is a prospective cohort study with a total of 7 follow-ups conducted within 4 weeks(4 followups?)<br><br>The tense – if the past tense is used, the manuscript sounds like a research paper and not a protocol paper.<br><br>Quality control - Investigators received standard operating procedure training before recruiting the patients.<br>What is standard operating procedure training?<br><br>Numerous grammatical and typing mistakes and choice of words. Some sentences are edited in the attached file.<br><br>The reviewer provided a marked copy with additional comments. Please contact the publisher fo full details. |

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| **REVIEWER** | Massimo Di Maio<br>Department of Oncology, University of Turin |
| **REVIEW RETURNED** | 16-May-2020 |

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| **GENERAL COMMENTS** | The topic of introduction of ePROs in clinical practice for cancer patients is timely and relevant. I appreciate the intention of the authors of performing a longitudinal study based on the use of PROs in patients with advanced cancer.<br>The protocol reports the details of this prospective study.<br>I have several comments:<br><br>1. Patients' inclusion is limited to some types of solid tumors. How is this limitation justified? (for instance, genito-urinary tumors are not included). I suppose that the limitation is related to the type of patients referred to the center. Please discuss.<br><br>2. if I understand well, only patients who are referred to the psychooncology unit are evaluated for the study. In my opinion, ePROs should be implemented for all patients treated in Oncology, authors should specify if this passage through Psychooncology is limited to the study or will be applied also later, to routine clinical practice.<br><br>3. who is going to manage (hopefully in real time) symptoms reported by patients? The psychooncologist or the Oncology personnel (physicians / nurses)? This should be better described<br><br>4.the paragraph of ePRO measures includes some items (ECOG PS, Charlson comorbidity index) that obviousluy are not PROs. This should be better specified and the structure of the paragraph could be modified accordingly.<br><br>5. I cannot understand the sample size calculation. The authors cite data (Cleeland) describing the burden of symptoms in lung cancer patients. Patients included in the study are 6 different tumor types (including also lung cancer). Which is the precision in the estimate of symptoms allowed by the sample size if the burden of symptoms is lower than 30%. Authors could describe the confidence interval according to different symptom prevalence (eg 20%, 30%, 40%) |

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| | 6. They have decided to use WeChat to vehiculate the ePROs. Does this imply some problems of privacy? ePROs platform should be certified to protect provacy. Please discuss.<br><br>7. It is not clear to me how the ePROs platform would interface with the patients' health records. In my opinion, the implementation of ePROs in clinical practice should discuss the incorporation of ePROs data into patients' electronic file (Marandino L, Necchi A, Aglietta M, Di Maio M. COVID-19 Emergency and the Need to Speed Up the Adoption of Electronic Patient-Reported Outcomes in Cancer Clinical Practice. JCO Oncol Pract. 2020 May 1:OP2000237. doi: 10.1200/OP.20.00237]. This issue should be discussed in the paper. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name: Christina Baggott
Institution and Country: Medical Research Institute of New Zealand
Please state any competing interests or state 'None declared': none declared

Please leave your comments for the authors below
Overview
This manuscript describes a protocol for an observational study investigating use of an electronic patient reported outcome platform into care of oncology patients in China. The intention is that such a system would allow improved symptom management. Overall I feel this study describes an innovative intervention that could benefit oncology patients by improving symptom management and leading to better care and outcomes.
Thank you for your overall comments of our study.

Major comments
I appreciate that writing in a language which is not your first language is difficult, however, in places incorrect use of tense, prepositions or adverbs etc. makes the meaning of some sentences more difficult to understand.
Thank you for your comments and we have modified the grammar and the wording of our manuscript.

Please could the authors clarify if this is a feasibility study to investigate the use of an electronic patient recorded outcome platform or was this data being used to change management and in what way? Was it integrated into patient records and would it be reviewed at the next clinic appointment or would worsening symptoms as captured by the ePRO prompt a more urgent review or a change in management or medication?
Thank you for your comments.

- Yes, this is a feasibility study to investigate the use of an electronic patient-reported outcome platform, and this data will provide guide to apply this novel platform in clinical practice of symptom management.
- So far this ePRO platform hasn't been investigated into patient records and the ePRO platform will send a notification to remind the patients who get worsen symptoms to visit the symptom management clinic as soon as possible.
- If the results of this study show this platform is feasible to use and is acceptable by the patients, our next goal is to integrate it into patient record and to be reviewed at the next clinic appointment. We hope this platform could prompt a more urgent review or a change in management or medication when worsening symptoms were captured by the ePRO.

The authors have mentioned there will be a qualitative component to understand why symptoms are not improving but they have not provided any details on the qualitative methodology. Please can they provide this information. For example would they use face to face interviews or focus groups, or will they be done over the phone? What is the analysis framework that will be used to analyse the qualitative data, will there be an interview guide and how was this developed?
Thank you for your comments.
We prefer a face to face interview, but if it is difficult for patients to come to the hospital, the interview could be done over the phone. The interview will be conducted follow an outline and be recorded then the recoded materials will be transcribed into words and be analyzed using a thematic analysis to develop a frame work of topics on causes of uncontrolled symptoms. We have added above details in the revised manuscript.

Minor comments
Abstract:
Please could you make the description of the primary outcome measure more explicit as I am not clear on what the authors mean by “the study of symptom burden”. Is the primary outcome to test the feasibility of collecting this data or is it to look for changes in symptom burden?
Thank you for your comments. We have clarified the primary outcomes as follows
“The primary outcomes are the changes on the intensity of the patients' target symptoms (including pain, fatigue, insomnia, anxiety, depression, nausea and vomiting) in 4 weeks after the initial visiting.”

Secondary outcomes – I am not clear what the authors mean by “reasons of no changes of symptom burden”. Are the authors expecting symptoms to be improving or getting worse? Are they just interested in patients whose symptoms are stable and not changing?
Thank you for your comments. We expect symptoms to be improved, because all these patients are seeking for help and being treated in the symptom management clinic. We are interested in patients whose symptom are failed to improved.

Strengths and limitations bullet points:
I am unclear if the study was 4 weeks long with follow up once a week how there would be 7 follow up episodes.
Thank you for your comments. The patients who visit symptom management clinic at the first time usually suffered one or more kinds of severe symptoms and will be given drug-therapy or non-drug therapy or both to address their symptoms. Usually in the first few days after their first visit, the symptoms will change rapidly. So we arrange 7 follow-up on Day 1, Day 3, Day 7, Day 10, Day 14, Day 21 and Day 28 after the first visit.

Introduction:
Page 9 the authors have commented that email is not widely used by the elderly in China, please could they clarify if is Wechat is used by this population? I am not sure that it is accurate to say in Western culture electronic application is mainly through
email.
It was reported the popularization rate of Wechat in China in 2018 was 87.3%, and according to our experiences, most of our patients, even elders can use Wechat. We also added this sentence to the introduction part.
To be more accurate, we changed that sentence to “In Western countries, some of the electronic applications are through e-mail”.
Page 9 I appreciate there are cultural differences between Chinese and Western culture, however, I think that the intervention that this study describes could be replicated in many countries allowing for the use of alternative mobile platforms, and the results would be widely applicable. I think this is a strength of this study which the authors may want to discuss.

Thank you for your comments, we have add the following words in our discussion part
“Although there are culture differences between Chinese and Western culture, the intervention that this study describes could be replicated in many countries allowing for the use of alternative mobile platforms, and the results would be widely applicable.”

Methods
Page 10 please clarify how are patients self-referred, was this through advertising or word of mouth?
Most patients are recommended by their oncologist to visit the symptom management clinic, some patients were recommended by other patients who had been treated in this clinic, while some patients saw advertisement of this clinic. And we have added this sentence in the “Study population and eligibility criteria and recruitment” part.

Page 10 more details on the inclusion and exclusion criteria are needed. For example please clarify if the patients are undergoing active treatment for cancer or palliative symptomatic management or a combination of both. This would help the reader understand who the patient population is.
Thank you for your comments, the patients include both patients undergoing active treatment for cancer and patients only having palliative symptomatic management. And we have added these details in the “Study population and eligibility criteria and recruitment” part.

Page 11 following primary objective I think pain has been missed from the list of target symptoms being monitored as it is present in the abstract.
Thank you for your comments, we have add “pain” into the list of target symptoms.

Page 12 what scoring scale was being used to measure pain and nausea and vomiting? Was this MDASI? Would a table listing the outcome measures and the symptoms they are measuring be clearer?
Thank you for your comments, we have added details about this “The target symptoms are measured by PRO instruments: pain and fatigue are measured by MDASI; depression is measured by HADS-D and PHQ-9; anxiety is measured by HADS-A; insomnia is measured by ISI and MDASI; nausea and vomiting is measured by MDASI.”

Page 12 please could the authors clarify what is meant by “the percentage of patients who met the eligibility criteria agreed to participate in the study is 80%”
Thank you for your comment, that sentence meant “At least 80% patients who met the eligibility criteria agreed to participate in the study.”

Page 13 outcome 3 the authors say semi-structured interviews will be conducted in patients whose symptom score improvement is less than 2, which scale dose this refer to and what about patients whose symptom scores worsen?
Thank you for your comments. We have changed that sentence to “Semi-structured interviews were conducted with patients whose symptom scores worsen or improved less than 2 points after 4 weeks.”

Page 13 please can the authors provide details on how the 5 additional items for specific cancer sites were selected, and what was the rationale for choosing these symptoms. For example I am unclear why constipation is specific to lung cancer but not other cancer sites?
Thank you for your comments, we have added the details about each additional item for which specific cancer sit, “ constipation is added to all cancers, hot flash and upper limb lymphedema is specific for breast cancer, cough is specific for lung cancer and swallowing difficulty is specific for esophagus cancer”.

Page 15 following the description of the ePRO platform it would aim the reader to see some screen shots of how the platform looked to patients and if possible provide an English translation.
We have add Figure 3, a screen shot to show how the platform looked to patients and we also provide an English translation directly in that figure.

Page 15 please provide information on how the information from the ePRO platform was integrated into the patients' care. Was it merged with the patients' hospital records? Did the data lead to a change in management? Did the patients receive earlier review or input from for example palliative care or pain specialists if they reported worsening pain?
Thank you for your comments.
- So far this ePRO platform hasn't been investigated into patient records and the ePRO platform will send a notification to remind the patients who get worsen symptoms to visit the symptom management clinic as soon as possible.
- If the results of this study show this platform is feasible to use and is acceptable by the patients, our next goal is to integrate it into patient record and to be reviewed at the next clinic appointment. We hope this platform could prompt a more urgent review or a change in management or medication when worsening symptoms were captured by the ePRO.

Reviewer: 2
Reviewer Name: Victor Chang
Institution and Country: VA New Jersey Health Care System
East Orange, NJ
USA
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
This is an interesting and important protocol. The authors need to pay more attention to details.
Thank you for your comments and we have modified this manuscript by adding a lot of details.

Major points
Primary purpose of the study is different in different parts of the protocol. Is it to measure symptom burden, or changes in symptom burden?
Thank you for your comments, the primary purpose of the study is to measure the changes in symptom burden, and we have made it consistent in different parts of the protocol.

Purposes of the study in the abstract, and in the introduction, and in the methods, are different for the secondary goals. Should be the same. In the introduction, secondary goals include "We also aim to examine the experience, acceptance and compliance of patients with the ePRO platform." In the methods and analysis, secondary goals are "feasibility of using ePRO, symptom related QoL, reasons for no changes of symptom burden, defining frequency of PRO assessments and cut-points, items for screening, and management of comorbidity." Under study objectives, secondary goal #7 is Analyzing the effects of co-morbidity and chronic diseases on symptom burden and symptom management of cancer patients.
Thank you for your comments. We have make the secondary goals consistent in different parts of the protocol.
In the introduction:
"The purpose of this study is to describe the changes of the symptoms of outpatients within 4 weeks after their first visit in the symptom management clinic and to test the feasibility to track patients' symptom changes through ePRO platform, to examine the impact of symptom changes on quality of life, to explore the causes of uncontrolled symptoms within four weeks; to determine the appropriate frequency, PRO items and alert score of PRO screening for different symptoms; to analyze the effects

of co-morbidity and chronic diseases on symptom burden and symptom management of cancer patients.

In the method:
"The second outcomes include as follow:
(1) Feasibility of tracking patients' symptoms changes with ePRO which contains two feasibility indexes:
1) At least 50% of patients completed self-report within 24 hours after being sent the follow-up message; more than 70% of patients completed self-report within 24 hours after being called; at least 70% of patients complete all self-reports within 4 weeks.
2) The percentage of patients who met the eligibility criteria agreed to participate in the study is 80%.
(2) The impact of changing trends of target symptoms intensity on quality of life over a 4-week period.
(3) The causes of uncontrolled symptoms with in 4 weeks.
(4) The appropriate frequency of PRO screening for different symptoms with the method of looking for significant changes in PRO scores (such as using generalized mixed effect model).
(5) The most appropriate PRO items for the targeted symptoms of the screening, with the optimal reliability and validity.
(6) The alert scores of PRO screening for different symptoms with clinical significance were determined by the criterion validity (such as EQ-5D) using the regression analysis model.
(7) The effects of co-morbidity and chronic diseases on symptom burden and symptom management of cancer patients."

Under study objectives:
"The second objectives are as follow:
(1) Evaluating the feasibility of tracking changes in target symptoms in outpatients through the ePRO follow-up system.
(2) Observing the improvement of quality of life in patients seeking symptom management in Department of Psycho-Oncology within 4 weeks after first visiting.
(3) Finding out the reasons why the symptoms of outpatients cannot be improved within 4 weeks after the first visiting through a qualitative research.
(4) Determining the appropriate frequency of PRO symptom screening through the description and analysis of the changes in patients' symptoms during the 4-week follow-up after first visiting.
(5) Exploring the most appropriate PRO items for the targeted symptoms of the screening.
(6) Determining the alert score of each PRO symptom through the analysis of the symptom changes during the follow-up 4 weeks after first visiting.
(7) Analyzing the effects of co-morbidity and chronic diseases on symptom burden and symptom management of cancer patients. "

Conclusion of the abstract - This study will provide a rational synthesis of current methods and evidences for using ePRO in psycho-oncology outpatient clinic – this type of conclusion is the result of a review paper.
Thank you for your comments, since many protocol manuscript doesn't have a conclusion part, so we delete the conclusion in the abstract.

Strengths and limitations - A relatively small sample size may be a limitation. – It is not a limitation if the sample size is properly calculated.
Thank you for your comments, we have deleted "A relatively small sample size may be a limitation".

Under data analysis, "the transcription of qualitative interview will be coded and

analyzed using NVivo 11.0." but a qualitative interview is mentioned only under study objectives #3 and then outcomes #3. The authors need a methodology paragraph where the 7 followups of the research subject are listed. This interview must be one of the followups

Thank you for your comments. We have revised the "Study design" part and added more details "This is a real-world, ongoing, longitudinal single-centre prospective study with a total of 7 follow-ups conducted within 4 weeks after the first visit of the symptom management clinic (on Day 1, Day 3, Day 7, Day 10, Day 14, Day 21 and Day 28). After the last follow-up, a semi-structured interview will be conducted with patients whose symptom scores worsen or improved less than 2 points after 4 weeks. "

There is no mention of how study subjects will be recruited, and consented.
All the eligible patients who visit the symptom management clinic at the first time will be invited to participant in this study by the doctors in this clinic. If the patients are interested in this study, a research assistant will inform this study to patients in detail and get their written inform consent. We have added above details of recruitment in our revised paper.

The authors identify target symptoms and different symptom instruments. Which instruments will be used to assess the target symptoms?
Thank you for your comments, we have added following details in the method part, "The target symptoms are measured by PRO instruments: pain and fatigue are measured by MDASI; depression is measured by HADS-D and PHQ-9; anxiety is measured by HADS-A; insomnia is measured by ISI and MDASI; nausea and vomiting is measured by MDASI."

There is no mention of how management of symptoms will be tabulated or analyzed. The only statement is that weChat can capture this information.
The ePRO platform could recognize the individual scores of MDASI items due to the cut-point that we set-up. For those scale that needed to be calculate for results, such as PHQ-9 are captured by WeChat first, saved in REDCap and calculated later.

Minor points
Strengths and limitations - The study is a prospective cohort study with a total of 7 follow-ups conducted within 4 weeks (4 followups?)
Thank you for your comments. The patients who visit symptom management clinic at the first time usually suffered one or more kinds of severe symptoms and will be given drug-therapy or non-drug therapy or both to address their symptoms. Usually in the first few days after their first visit, the symptoms will change rapidly. So we arrange 7 follow-up on Day 1, Day 3, Day 7, Day 10, Day 14, Day 21 and Day 28 after the first visit.

The tense – if the past tense is used, the manuscript sounds like a research paper and not a protocol paper.
Thank you for your comments, we have modified the past tense into present or future tense.

Quality control - Investigators received standard operating procedure training before recruiting the patients.
What is standard operating procedure training?
Thank you for your comments, we have modified the "Quality control" part as follows,
"Investigators received standard operating procedure training before recruiting the patients. A standardized operation process manual and an operation video has been made and distributed to all the research assistant. The Group training was organized for one time while individual (one-to-one)

training were carried out one-to-one. After the training, all research assistants required to pass a test of practical operation to getting start on their official work.
There will be a Question & Answer session to solve operation problems after around 10 cases enrolled. In addition, the practical problems that faced by research assistants will be shared in WeChat working group at any time. ”

Numerous grammatical and typing mistakes and choice of words. Some sentences are edited in the attached file.
Thank you very much for editing the manuscript for us.

Reviewer: 3
Reviewer Name: Massimo Di Maio
Institution and Country: Department of Oncology, University of Turin
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
The topic of introduction of ePROs in clinical practice for cancer patients is timely and relevant. I appreciate the intention of the authors of performing a longitudinal study based on the use of PROs in patients with advanced cancer.
The protocol reports the details of this prospective study.
I have several comments:

1. Patients' inclusion is limited to some types of solid tumors. How is this limitation justified? (for instance, genito-urinary tumors are not included). I suppose that the limitation is related to the type of patients referred to the center. Please dis

Thank you for your comments. The patients inclusion is limited to six cancer types including liver cancer, gastric cancer, esophageal cancer, colorectal cancer and breast cancer, the reason we choose these six cancer types is because they are the top six cancer types in China and also covered most of the cancer patients in our clinic.

2. if I understand well, only patients who are referred to the psychooncology unit are evaluated for the study. In my opinion, ePROs should be implemented for all patients treated in Oncology, authors should specify if this passage through Psychooncology is limited to the study or will be applied also later, to routine clinical practice.
Thank you for your comments and we agree with your comments that ePROs should be implemented for all patients treated in Oncology. If the results of this study show this platform is feasible to use and is acceptable by the patients, our next goal is to integrate it into patient record and to be implemented for all patients. We hope this platform could prompt a more urgent review or a change in management or medication when worsening symptoms were captured by the ePRO.

3. who is going to manage (hopefully in real time) symptoms reported by patients? The psychooncologist or the Oncology personnel (physicians / nurses)? This should be better described
This study doesn’t include intervention, we hope in the future, the PRO platform will be integrated into the patient record and be reviewed by the psycho-oncologists in real time and they can manage the symptoms in time.

4.the paragraph of ePRO measures includes some items (ECOG PS, Charlson comorbidity index) that obviousluy are not PROs. This should be better specified and the structure of the paragraph could be modified accordingly.

Thank you for your comments. Yes, ECOG PS, Charlson comorbidity index are not PROs.
We have modified these part as follows
" Totally 9 study instruments are used in this study, including 6 PRO instruments.
(1) PRO instruments
MD Anderson Symptom Inventory, MDASI.
MDASI [8][9] is a widely used symptom inventory with 19 items (13 items for symptom severity, 6 items for interference), 0=Nothing, 10=Most severity. Psychometric study has shown that the Chinese version of MDASI has good reliability and validity, so that the Chinese MDASI can be used to measure the severity of multiple symptoms and their impact on function in Chinese cancer patients. Moreover, we have added 5 more items for specific cancer sites in our study to capture special characteristics: "constipation" and "cough" for lung cancer; "dysphagia for gastrointestinal cancer"; "hot flashes and upper extremity edema for breast cancer". A single "quality of life" item was used to anchor this study.
Insomnia Severity Index, ISI
It is a validated scale for measuring insomnia severity in the last tow weeks. There are total 7 items, 0-4 score for each item, with the sum score of 0-28. 0-7 score indicates no insomnia; 8-14 score indicates subclinical insomnia; 15-21 score indicates moderate insomnia, 22-28 score indicates severe insomnia. Simplified Chinese version of ISI has been validated by Lin et al [10].
Hospital Anxiety and Depression Scale, HADS
HADS has 14 items with a score spectrum of 0-4 for each item, which is used to measure the anxiety and depression for the patients in the past week. It is used for patients with somatic symptoms in the general hospitals with good reliability and validity and recommended for patients with advanced cancer or receiving palliative care [11].
9 Item Patient Health Questionnaire, PHQ-9
PHQ-9 is used to evaluate the depression of patients in the past two weeks. The score spectrum of symptoms severity is from 0=none at all to 3=almost every day, and the total score was from 0-27. Depression can be considered when the sum score is ≥10. Simplified Chinese version of PHQ-9 has a good validation [12].
EuroQol Five Dimensions questionnaire-5L version, EQ-5D-5L
EQ-5D-5L is a multidimensional measurement for health-related quality of life, which contains these five domain to describe patients' health: 1) mobility; 2) self-care; 3) usual activities; 4) pain/discomfort; 5) anxiety/depression, with a scale from 0=No difficulty to 4=extremely difficulty [13]][14]
Distress Thermometer, DT
DT is recommended by NCCN in the distress management guideline and was introduced to China in 2007. DT has only one item with a scale from 0=No distress to 10=extreme distress. Problem list including 5 domains: practical problem, communication problem, emotion problem, physical problem, spirit and religion problem. It is recognized as the briefest tool for distress screening, especially in busy oncology clinical practice [15].
The target symptoms are measured by PRO instruments: pain and fatigue are measured by MDASI; depression is measured by HADS-D and PHQ-9; anxiety is measured by HADS-A; insomnia is measured by ISI and MDASI; nausea and vomiting is measured by MDASI.
(2) General demographic and disease data questionnaire.
General demographic data includes age, sex, occupation, etc. The latter includes disease diagnosis, staging, treatment, medication, etc.
(3) ECOG score.
This is a health tool that evaluates cancer patient functional status and clinically stratifies these patients` ability to tolerate therapies, which runs from 0 to 5, with 0 denoting perfect health and 5 death [16].
(4) Charlson Comorbidity Index.
Comorbid conditions are best evaluated with use of the Charlson Comorbidity Index. Many studies have shown that the impact of comorbidities is significant on the survival outcomes and prognosis of cancer patients. Here are the conditions used in the comorbidity and the number of points they are

awarded: score of 1 for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, and diabetes mellitus(in terms of diabetes mellitus, score of 1 for uncomplicated and 2 for end organ damage); score of 2 for moderate to severe chronic kidney disease, hemiplegia, leukemia, malignant lymphoma, solid tumor(2 in case of presence and 6 in case tumor is metastatic), liver disease(mild 1 point, moderate to severe 3 points) and AIDS [17]. ”

5. I cannot understand the sample size calculation. The authors cite data (Cleeland) describing the burden of symptoms in lung cancer patients. Patients included in the study are 6 different tumor types (including also lung cancer). Which is the precision in the estimate of symptoms allowed by the sample size if the burden of symptoms is lower than 30%. Authors could describe the confidence interval according to different symptom prevalence (eg 20%, 30%, 40%).
Thank you for your comment, the statistician in our team calculated the 95% confidence interval according to different symptom prevalence: 40%, 32.11-47.89%; 30%, 22.62-37.38%; 20%, 13.56-26.44%. We have add them in the sample size calculation part.

6. They have decided to use WeChat to vehiculate the ePROs. Does this imply some problems of privacy? ePROs platform should be certified to protect provacy. Please discuss.

Thank you for your comment, we totally agree with you that the information security is very important. Information of completion progress would be shown on the physician sites. Each response on WeChat requires an authorized security token to be submitted, a secure network connection ensures that collected responses were only sent to the database established in Beijing Cancer Hospital. The ePRO and data transmission network were reviewed and approved by the information security engineer of Beijing Cancer Hospital.

7. It is not clear to me how the ePROs platform would interface with the patients' health records. In my opinion, the implementation of ePROs in clinical practice should discuss the incorporation of ePROs data into patients' electronic file (Marandino L, Necchi A, Aglietta M, Di Maio M. COVID-19 Emergency and the Need to Speed Up the Adoption of Electronic Patient-Reported Outcomes in Cancer Clinical Practice. JCO Oncol Pract. 2020 May 1:OP2000237. doi: 10.1200/OP.20.00237]. This issue should be discussed in the paper.

Thank you for your comments.

So far this ePRO platform hasn’t been investigated into patient records and the ePRO platform will send a notification to remind the patients who get worsen symptoms to visit the symptom management clinic as soon as possible.

If the results of this study show this platform is feasible to use and is acceptable by the patients, our next goal is to implement ePRO into clinical practice by integrate it with patient‘s electronic health record. We hope this platform could be helpful for clinicians to capture their patients' symptom change in-time and offer a more flexible symptom/ medication management when worsening symptoms were developed.

We totally agree with you that it is urgent to incorporate ePRO into patients’ electronic health record. ePRO platform could be a useful tool to monitor and manage the patients’ symptoms at home.
We have added above part in the discussion and also with the literature you recommended.

## VERSION 2 – REVIEW

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|---|---|
| **REVIEWER** | Victor Chang<br>VA New Jersey Health Care System<br>East orange, NJ USA |
| **REVIEW RETURNED** | 06-Aug-2020 |

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| **GENERAL COMMENTS** | Manuscript improved.<br>Still overly ambitious.<br>Comments in attached file<br>Need editing for grammar and word choice<br><br>The reviewer provided a marked copy with additional comments.<br>Please contact the publisher fo full details. |

| | |
|---|---|
| **REVIEWER** | Massimo Di Maio<br>Department of Oncology, University of Turin; Ordine Mauriziano Hospital, Turin, Italy. |
| **REVIEW RETURNED** | 05-Aug-2020 |

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|---|---|
| **GENERAL COMMENTS** | The authors modified the manuscript according to my suggestions (and other Reviewers' comments). Most of the issues have been clarified.<br>I have only one suggestion: in the sample size paragraph "The 95% confidence interval according to different symptom prevalence are 40%, 32.11-47.89%; 30%, 22.62-37.38%; 20%, 13.56-26.44%. To obtain a 95% confidence interval as 22%-38%, we will need 148 evaluable patients.", maybe it is more clear to invert the 2 sentences, considering that the sample size has been calculated for a 30% hypothesis. |

## VERSION 2 – AUTHOR RESPONSE

Reviewer: 3
Reviewer Name: Massimo Di Maio
Institution and Country: Department of Oncology, University of Turin; Ordine Mauriziano Hospital, Turin, Italy.
Please state any competing interests or state ‘None declared’:None declared

Please leave your comments for the authors below
The authors modified the manuscript according to my suggestions (and other Reviewers' comments). Most of the issues have been clarified.
I have only one suggestion: in the sample size paragraph "The 95% confidence interval according to different symptom prevalence are 40%, 32.11-47.89%; 30%, 22.62-37.38%; 20%, 13.56-26.44%. To obtain a 95% confidence interval as 22%-38%, we will need 148 evaluable patients.", maybe it is more clear to invert the 2 sentences, considering that the sample size has been calculated for a 30% hypothesis.
Thank you for your good suggestion. We have inverted the 2 sentences and the revised version is “To obtain a 95% confidence interval for 30%, we will need 148 evaluable patients, which was according

to different symptom prevalence for 40%, 32.11-47.89%; 30%, 22.62-37.38%; 20%, 13.56-26.44%." (Page 17)

Reviewer: 2
Reviewer Name: Victor Chang
Institution and Country: VA New Jersey Health Care System, East orange, NJ USA
Please state any competing interests or state 'None declared':None
Please leave your comments for the authors below
Manuscript improved.
Still overly ambitious.
Comments in attached file
Need editing for grammar and word choice

1. These are a wide variety of outcomes. It can be part of your specific objectives that you want to accomplish these goals. The outcome for the ePRO could include patient acceptance, participation, satisfaction with the platform. Health care provider satisfaction with the platform.
Thank you for your comments and good suggestions, the patient acceptance, participation could be indicated by feasibility outcomes presented as follows (Page 9).
"The second objectives are as follow:
(1) Evaluating the feasibility of tracking changes in target symptoms in outpatients through the ePRO follow-up system.
1) At least 50% of patients completed self-report within 24 hours after being sent the follow-up message; more than 70% of patients completed self-report within 24 hours after being called; at least 70% of patients complete all self-reports within 4 weeks.
2) The percentage of patients who met the eligibility criteria agreed to participate in the study is 80%. "
And we could add a satisfactory interview by focus group with patients and health provides.
And we added " (8) To explore the satisfaction with ePRO platform in patients and health provider by an focus group interview." (Page 10)
In abstract we have added "…and satisfaction with ePRO platform in patients and health providers."

2. On p2, state 7 follow-ups in 4 weeks
Thank you for pointing out this error. Yes, there are 7 follow-ups in 4 weeks, so we changed "……sends ePRO follow-up notification weekly for 4 weeks" to "sends ePRO follow-up notification 7 times over 4 weeks". (Page 4)

3. What is the sample size needed to be able to make these determinations? You may have enough data to make an initial estimate, but this may change with more patients in the future
The feasibility is not our primary outcome so the sample size was not calculated based on this outcome, and we have no enough data on the feasibility but we hope our study could provide enough data to determine the sample size in the future study.

4. Concerns is whether patients will want to fill out all these questionnaires.
Actually, the burden for patients to fill the questionnaires were not that heavy. The patients need to fill all the questionnaires only for three times at the baseline assessment, Day 14 and Day 28 follow-up. At other follow-ups, patients only need to fill MD Anderson Symptom Inventory with only 19 items. (Page 11) The patient recruitment are done by physicians in symptom management clinic. The physicians will invite the patients to participant in the survey, and tell the patients that follow-ups can let the physicians know about their conditions and it will benefit their symptom management.

5. “The purpose of this study is to test the feasibility to track patients’ symptom changes through ePRO platform, describe the changes of the target symptoms (pain, insomnia, fatigue, anxiety, depression, nausea and vomiting) of outpatients within 4 weeks after their first visit in the symptom management clinic and to examine the impact of symptom changes on quality of life, to determine the appropriate frequency, PRO items and alert score of PRO screening for different symptoms.” Similar to objectives below.
Thank you for pointing out this, and I have deleted this paragraph and kept the objectives below.

6. “This is a real-world, ongoing, longitudinal single-center prospective study with a total of 7 follow-ups conducted within 4 weeks.” Is it 4 or 7 follow-ups?
Thank you for comments. 7 is right, there should be 7 follow-ups during 4 weeks.

7. “After the last follow-up, a semi-structured interview will be conducted with patients whose symptom scores worsen or improved less than 2 points after 4 weeks.” Why not all the patients? Because we would like to know about the reasons for why some symptoms could not be improved within 4 weeks.

8. “poor physical condition, judged by the attending physician, not suitable for participating in the study” These will be the patients with the most symptoms and the most changes.
Thank you for your comments. Sorry for my unclear description. I mean the patients who can’t use the ePRO platform due to their poor physical or mental conditions. So we changed the item to “poor physical or mental condition, judged by the attending physician, not able to complete the whole study;” (Page 8-9)

9. ECOG score is done by doctors.
Yes, it is done by doctors, and we added “this measure is done by doctors.”(Page 13)

10. “Charlson Comorbidity Index” Is this determined from chart review by the team or completed by the patient.
It is determined from chart review. And we have added “It is determined by chart review.” (Page 13)