PEER REVIEW HISTORY

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This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Lung Cancer App (LuCApp) study protocol: a randomised controlled trial to evaluate a mobile supportive care app for patients with metastatic lung cancer
AUTHORS	Ciani, Oriana; Cucciniello, Maria; Petracca, Francesco; Apolone, Giovanni; G., Merlini; Novello, Silvia; Pedrazzoli, Paolo; Zilembo, Nicoletta; Broglia, Chiara; Capelletto, Enrica; Garassino, Marina; Nicod, Elena; Tarricone, Rosanna

VERSION 1 – REVIEW

REVIEWER	Catherine Huggins Monash University, Australia
REVIEW RETURNED	12-Aug-2018

GENERAL COMMENTS	This paper reports a study protocol for a randomized open-controlled trial testing the effectiveness and cost effectiveness of an App (LuCApp) to support symptom management of people undergoing treatment for lung cancer. The proposed study is important as it seeks to investigate if mHealth can enable patients to self-manage their symptoms during cancer treatment and hence improve health outcomes compared with the standard care only. The intervention period is 24 weeks and primary outcome (HRQoL) assessment occurs at 12 weeks. Some minor changes to the manuscript are suggested to improve the clarity and transparency to permit replication of the study. Abstract - The Abstract states the primary outcome is at 12 weeks, whereas the main text indicates 12 weeks and 24 weeks. Are both primary outcomes i.e has the study been powered to see a difference at both times? Will the primary analysis include both time points in the statistical testing? - The Abstract could end with a sentence summing up what the expected impact of this study will be. Objectives - The list of outcomes state the predicted change therefore, is this a list of hypotheses rather than a list of objectives? Randomisation: - page 12, line 13: should this state that "participants remain in the study until the end of the 24 week intervention period unless

	early withdrawal occurs due to discontinuation of cancer treatment, voluntary… Blinding - Although it's not practical to blind the patients or researchers who deliver the intervention, will the researchers be blinded from the outcome data until the end of the of the study? If not, why not? How are the patient-reported data downloaded from the App? If the clinician-researchers are able to see the HRQoL scores during the intervention period this may result in a change in their behavior (e.g how quickly they respond to patients). Page 13, line 33 Will patients be made aware that a symptom rating of 3 or more will trigger an alert to the health Professionals? Will patients be coached/ trained not to escalate the symptoms unnecessarily, or conversely encouraged not to avoid rating over 3 when it is necessary (i.e some people may not want to "burden" the health care professionals?). Page 14, line 33 write his/her Page 14, line 48 As this study seeks to determine cost-effectiveness, it will be necessary to capture clinician time. How will this be recorded in the control and intervention groups. More detail is required on how resource use data (page 19) are to be collected. Page 15, line 50 Will emergency department visits be documented for incorporation into the cost evaluation and if so how will this data be collected? Page 16, line 4: replace telephonic with telephone. Page 21, line 44, how much power will this study have to examine survival? Page 23, should the names of the ethics committees be included in the statement?

REVIEWER	Jennifer Jupp Alberta Health Services - Calgary, Alberta, Canada
REVIEW RETURNED	14-Aug-2018

GENERAL COMMENTS	To the investigators. Thank you for the opportunity to review your protocol. Your research is exciting and innovative. It is wonderful to see research in the are of mHealth and it's impact on measurable patient outcomes. I had two issues for your consideration: 1. Will the use of oral chemotherapy agents be included in your study? If so, does the app assist with medication tracking and adherence? Will adherence be assessed in both arms? 2. Will the promotion of the use or trouble shooting take place during clinic visits? If patients do not use the app for >3 days and ignore reminders, will the investigators encourage it's use? I understand there will be an introduction to the app, but will follow-up occur to ensure patients are self-reporting correctly or to assess if patients are having troubles using the app? Good luck with your research!

REVIEWER	STEPHEN AGBOOLA PARTNERS CONNECTED HEALTH, USA
REVIEW RETURNED	20-Aug-2018

GENERAL COMMENTS	This is a manuscript of the protocol for a 2-arm RCT to evaluate the impact of a mobile supportive care app for patients with metastatic lung cancer on HRQoL. The manuscript is well-written. The authors have done a great job of describing the study design and procedures. I have some minor comments below. 1. Pg 9, study settings: what types of hospitals (tertiary, secondary, etc) are the 3 three oncologic sites? Is the level of care the same across all three sites? Please include a statement about the comparability of care across all three sites. 2. Pg 10, line 18- 31: Baseline questionnaires will be completed on paper by all participants. The next paragraph starting line 22 refers to another set of questionnaires. I 'm assuming these are follow-up questionnaires. So, please clarify. These questionnaires are to be completed via the app in the intervention group whereas it was paper/telephone-based in the control group. Some studies have shown that there is a difference in response rates, missing data, etc for app vs paper-based data collection techniques. The approach taken in this study may result in some systematic differences in responses to the questionnaires. 3. Randomization: after consent and completion of paper-based baseline questionnaires, how do participants access the electronic case report form for their randomization code? Please include detailed description of events (under assignment of interventions in attached SPIRIT document) leading up to allocation assignments. Did the participants receive help from study staff? Also, who enrolled participants into the study? 4. What happens at study closeout? It is unclear whether this visit happens virtually or in-person. Some questionnaires are administered via the app for the intervention while others are administered in paper formats (e.g. ZBI). It is unclear how the SCNS-SF34 will be administered? Also, will intervention participants continue to use app after closeout? 5. Analysis: app use is hypothesized to drive the desired effect in this study. App utilization data (frequency, duration of use, features visited, etc) are being collected. So, there's opportunity to evaluate the impact of app use (level of engagement) on study outcomes. 6. Please correct minor typos which are scattered over the document in the next round of revisions.

VERSION 1 – AUTHOR RESPONSE

	Reviewers' Comments	Authors' reply	Modifications made on the manuscript
1	Reviewer 1		

1.0	This paper reports a study protocol for a randomized open-controlled trial testing the effectiveness and cost effectiveness of an App (LuCApp) to support symptom management of people undergoing treatment for lung cancer. The proposed study is important as it seeks to investigate if mHealth can enable patients to selfmanage their symptoms during cancer treatment and hence improve health outcomes compared with the standard care only. The intervention period is 24 weeks and primary outcome (HRQoL) assessment occurs at 12 weeks. Some minor changes to the manuscript are suggested to improve the clarity and transparency to permit replication of the study.	Thank you for your encouraging feedback!	-
1.1	Abstract - The Abstract states the primary outcome is at 12 weeks, whereas the main text indicates 12 weeks and 24 weeks. Are both primary outcomes i.e. has the study been powered to see a difference at both times? Will the primary analysis include both time points in the statistical testing? The Abstract could end with a sentence summing up what the expected impact of this study will be.	Thank you for raising this point. The primary outcome is the change in the score of the Trial Outcome Index (TOI) in the Functional Assessment of Cancer Therapy (Lung) questionnaire from baseline to 12 weeks. However this outcome and secondary outcomes will be collected for the entire duration of the study, up to 24 weeks.	In the Abstract, we added: "Conclusions: This trial makes a timely contribution to test a mobile application designed to improve the quality of life and delivery of care for patients with lung cancer." At page 8 then: "The primary objective of the study will be to determine whether LuCApp […] can lead to increased HRQoL scores as measured by the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire (13) from the start of the

			pharmacological treatment for lung cancer and up to 12 weeks

			(primary endpoint) and 24 weeks follow-up."
1.2	Objectives - The list of outcomes state the predicted change therefore, is this a list of hypotheses rather than a list of objectives?	Thank your for raising this point. We clarified this element in the text.	At page 8: "More specifically, the hypotheses made on the impact attainable through the app were:…"
1.3	Randomisation - page 12, line 13: should this state that "participants remain in the study until the end of the 24 week intervention period unless early withdrawal occurs due to discontinuation of cancer treatment, voluntary…	Thanks again, the sentence was not accurate and has been rephrased.	At page 11: "Participants will remain into the study until the end of the 24 week intervention period unless early discontinuation occurs due to cessation of cancer treatment, voluntary withdrawal or death."
1.4	Blinding - Although it's not practical to blind the patients or researchers who deliver the intervention, will the researchers be blinded from the outcome data until the end of the of the study? If not, why not? How are the patient-reported data downloaded from the App? If the clinicianresearchers are able to see the HRQoL scores during the intervention period this may result in a change in their behavior (e.g.	Thanks for this comment. The clinician version of LuCApp allows the researchers to monitor the symptoms presence and severity but not the HRQoL questionnaires completed by the patients. The Android and iOS versions of the app (patient version) serve as a data capture interface that collects and transfers data, under https security protocol, to the database behind the electronic data capture platform. We have now clarified both aspects in the text.	At page 11: "However, the clinician version of LuCApp does not allow the doctors to monitor HRQoL questionnaires completed by the patients…" At page 12: "The Android and iOS versions of the app (patient version) serve as a data capture interface that collects and transfers data, under https security protocol, to the database behind the

	how quickly they respond to patients).		electronic data capture platform."
1.5	Page 13, line 33 Will patients be made aware that a symptom rating of 3 or more will trigger an alert to the health Professionals? Will patients be coached/ trained not to escalate the symptoms unnecessarily, or conversely encouraged not to avoid rating over 3 when it is necessary (i.e. some people may not want to "burden" the health care professionals?)	Thank you for pointing out this specific detail. We have clarified the description of our methodology. Patients will be made aware that a rating of 3 or more will trigger an alert to the health professionals by the research nurse during the training session that will be held during the enrollment visit. Detailed information will be provided to patients by the research nurse about the use of the app and the relevance to fill in truthful information and use the tool in an appropriate way. Furthermore, to prevent patients from escalating symptoms unnecessarily, we included a detailed description for each side effect and each option was matched with a description adapted for patient use from the Common Terminology Criteria for Adverse Events (CTCAE). As a result, patients will not have to answer exclusively on a scale from 0 to 4 (where 0 is symptom not present, 4 is maximum degree of severity) but they are	At page 11 we clarified: "At this stage, patients will receive adequate training and detailed information about the app usage by the research staff, including research nurses, data mangers and oncologists, who will also help patients download the application on their own device". At page 13 we pointed out: "Patients will be aware that reporting symptoms above that threshold will produce an alert to the clinicians: in order to elicit truthful answers, we included for each symptom a detailed

		helped by options that practically exemplify what each value entails.	description and a set of options with specific criteria referred to the exact grade listed in the CTCAE."
1.6	Page 21, line 44, how much power will this study have to examine survival?	Thank you for raising this question. Assuming a 70% survival in the control group, we calculated that this study will have 80% power and 5% significance level to detect an hazard ratio of 0.26 at the end of the study.	-

1.7	Page 14, line 48 As this study seeks to determine cost-effectiveness, it will be necessary to capture clinician time. How will this be recorded in the control and intervention groups. More detail is required on how resource use data (page 19) are to be collected.	We agree with the reviewer this aspect requires further clarification. The eCRF includes an entire section dedicated to healthcare resource consumption that captures diagnostic and instrumental tests performed, medicines and dietary supplements taken, GP and specialists visits undertaken, hospitalisation and emergency access occurred between study visits. This is captured for both study arms. In order to quantify average per-patient medical doctor time dedicated to LuCApp vs usual care management of lung cancer treatment related symptoms, a questionnaire will be administered to clinicians at different time points throughout the study.	At page 19: "Resource use will be captured through patients' reports of symptoms and clinicians actions in response to those symptoms (e.g. prescriptions, hospitalisations including emergency access, change in therapy). Moreover, additional information will be obtained for both control and treatment group patients via a form administered during the clinics on instrumental and diagnostics tests performed, GP or specialist visits, additional medicines or dietary supplements taken, hospitalisation or emergency access occurred between visits. Average perpatient clinician time spent for LuCApp management or standard care management of lung cancer therapies' symptoms will be elicited with questionnaires administered to the clinicians at different time points during the study."
1.8	Page 15, line 50 Will emergency department visits be documented for incorporation into the cost evaluation and if so how will this data be collected?	See above.	-
1.9	Page 14, line 33 write his/her Page 16, line 4: replace telephonic with telephone.	Thank you. Edits made.	-

1.10	Page 23, should the names of the ethics committees be included in the	Thank you. The three ethics committees are now explicitly reported in the text.	At page 22: “The trial received ethical approval

	statement?		from the ethics committees at the three clinical sites: Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo, Fondazione IRCCS Istituto Nazionale dei Tumori and Azienda Ospedaliero-Universitaria San Luigi Gonzaga.”
2	Reviewer 2		
2.0	Thank you for the opportunity to review your protocol. Your research is exciting and innovative. It is wonderful to see research in the area of mHealth and its impact on measurable patient outcomes. I had two issues for your consideration.	Thank you for this enthusiastic feedback!	-
2.1	Will the use of oral chemotherapy agents be included in your study? If so, does the app assist with medication tracking and adherence? Will adherence be assessed in both arms?	Following the reviewer’s comment, we better clarified one relevant aspect of this study. Patients eligible for chemotherapy, immunotherapy and targeted therapies will be included in the study. Consequently, patients undergoing oral therapies at home may be included in the study. However, the intervention app does not feature any specific medication tracking or reminder tool that support the adherence to treatment of this group of patients. Since these patients still routinely meet their cancer care team, no impact is anticipated on the data collection process for standard of care patients.	Page 14, the following sentence was added: “As a direct consequence, although the inclusion of targeted therapies as well as chemotherapies may imply that some patients will be undergoing oral treatments at home and not in hospitals or clinics, the app does not aim at managing, at least not directly, medication adherence.”

2.2	Will the promotion of the use or trouble shooting take place during clinic visits? If patients do not use the app for >3 days and ignore reminders, will the investigators encourage it's use? I understand there will be an introduction to the app, but will followup occur to ensure patients are selfreporting correctly or to assess if patients are having troubles using the app? Good luck with your research!	Thanks for raising this point. The promotion of the use of the app and the resolution of any type of issue will happen during clinic visits. However, other options will be available as well. Patients will be assisted during the whole study period by a technical "helpdesk" and they can refer to it for any type of questions/issues they would encounter. Furthermore, the Data Manager or another member of the research team at each site will regularly check upload of data from the intervention group and be in contact by email or phone to see if there are technical problems and to encourage app use.	Page 11, we specified: "Furthermore, the Data Manager will regularly check upload of data from the intervention group and the research team will be in contact by email or phone to verify if there are technical problems and to encourage app use."
3	Reviewer 3		
3.0	This is a manuscript of the protocol for a 2-arm RCT to evaluate the impact	Thank you for your encouraging feedback!	-

	of a mobile supportive care app for patients with metastatic lung cancer on HRQoL. The manuscript is wellwritten. The authors have done a great job of describing the study design and procedures. I have some minor comments below.		
3.1	Pg 9, study settings: what types of hospitals (tertiary, secondary, etc) are the 3 three oncologic sites? Is the level of care the same across all three sites? Please include a statement about the comparability of care across all three sites.	Thank you for asking for this clarification. Two of these centers are highly specialized centers (IRCCS), of which one is entirely dedicated to oncology (INT). The third center is a teaching hospital. The care provided is aligned with the guidelines developed by the Italian Association of Medical Oncology (AIOM). Patients are allowed to contact their sites for concerning symptoms that occur between scheduled visits or advised to see the out-of-hour doctor. An emergency department is available at San Matteo Hospital and San Luigi Gonzaga Hospital, nut not at INT. These elements have been included in the text.	At page 15: "Participating centers are either research dedicated hospitals (San Matteo Hospital, Istituto Nazionale Tumori) or teaching hospital (San Luigi Gonzaga Hospital). […] Patients are usually allowed to contact their sites for concerning symptoms that occur between scheduled visits or advised to see the out-of-hour doctor. An emergency department is available at San Matteo Hospital and San Luigi Gonzaga

			Hospital, but not at Istituto Nazionale Tumori.”
3.2	Pg 10, line 18- 31: Baseline questionnaires will be completed on paper by all participants. The next paragraph starting line 22 refers to another set of questionnaires. I‘m assuming these are follow-up questionnaires. So, please clarify. These questionnaires are to be completed via the app in the intervention group whereas it was paper/telephone-based in the control group. Some studies have shown that there is a difference in response rates, missing data, etc for app vs paperbased data collection techniques. The approach taken in this study may result in some systematic differences in responses to the questionnaires.	After completion of paper questionnaires at baseline, LucApp arm patients will fill in follow-up questionnaires via the app, while control patients will fill in follow-up questionnaires in paper or via phone. The reviewer rightly points out this potentially could affect response rates and missing data levels. We acknowledge this in the limitations.	At page 24: “Moreover, different modes of questionnaires administration (appbased vs paper/phone-based) may result in different response rates and missing data across the two arms, although monitoring of outcomes collection at pre-specified time points will occur for both intervention and control groups.”
3.3	Randomization: after consent and completion of paper-based baseline	The recruitment will be responsibility of the research team at each site, including research nurses, data managers and	At page 10: “Once informed consent has been

	questionnaires, how do participants access the electronic case report form for their randomization code? Please include detailed description of events (under assignment of interventions in attached SPIRIT document) leading up to allocation assignments. Did the participants receive help from study staff? Also, who enrolled participants into the study?	oncologists. It is one of these figures (mainly research nurses) that will obtain the randomization code generated electronically via a web-based platform. This element is now clarified in the text.	received and baseline PROMs collected, the research staff dedicated to the recruitment will obtain a randomisation code, from randomly permutated blocks stratified by site and therapy (i.e. chemotherapy, immunotherapy and targeted therapy), generated electronically and assigned to the patient via a secure web-based electronic case report form."
3.4	What happens at study closeout? It is unclear whether this visit happens virtually or in-person. Some questionnaires are administered via the app for the intervention while others are administered in paper formats (e.g. ZBI). It is unclear how the SCNS-SF34 will be administered? Also, will intervention participants continue to use app after closeout?	Thank you very much for pointing this out. To clarify how study close-out will work, a specific paragraph has been added to the manuscript. With respect to the SCNS-SF34, it is included in LuCApp and therefore can be completed digitally for the intervention group patients.	Page 20, the "Study close-out" paragraph was added: "At study closeout at week 24, patients in the intervention arm will not continue to use the app and will be lead back to standard of care. They will fill all PROMs in through the app, while for standard of care patients PROMs will be collected in the hospital during an ad-hoc closing visit. As for the Zarit Burden Interview, which will be administered to the main caregiver at the end of the study, it will be completed either in person or via phone."
3.5	Analysis: app use is hypothesized to drive the desired effect in this study. App utilization data (frequency, duration of use, features visited, etc) are being collected. So, there's opportunity to evaluate the impact of app use (level of engagement) on study outcomes.	Thank you for this comment. Indeed we agree that use and adoption metrics are important to understand the mechanism of action of such intervention. The mHealth application contains a tracking system through which frequency and duration of logins and the activity will be recorded. A secondary per protocol analysis is planned that will take into account the influence of use and adoption metrics on study outcomes.	-
3.6	Please correct minor typos which are scattered over the	Thank you. We conducted a careful proofreading of the revised version of the manuscript.	-

	document in the next round of revisions.		

VERSION 2 – REVIEW

REVIEWER	Catherine Huggins Monash University, Australia I am currently undertaking research that is examining ways to use mHealth for supporting people undergoing treatment for upper GI cancer.
REVIEW RETURNED	17-Nov-2018

GENERAL COMMENTS	Thank you for your clear response and modifications to the manuscript.

REVIEWER	STEPHEN AGBOOLA Harvard Medical School, USA
REVIEW RETURNED	13-Nov-2018

GENERAL COMMENTS	This is a revised manuscript describing the protocol for a 2-arm RCT to evaluate the impact of LUCapp, a mobile supportive care app for patients with metastatic lung cancer on HRQoL, usability and resource utilization. The authors did a nice job addressing all the reviewers' comments. The manuscript is much improved by the revisions made. However, a minor sticky needs to be addressed. Page 11, description of intervention: line 54 "…research team will be in contact…". Is this ongoing contact (for troubleshooting and reminding) just for the purpose of this research or is this what would happen during implementation? This human resource effort would need to be accounted for in the cost/resource use analysis if not already planned. Also, to ensure that the study is replicable, please include the frequency of these calls as part of intervention procedures?

VERSION 2 – AUTHOR RESPONSE

	Reviewers' Comments	Authors' reply	Modifications made on the manuscript
1	*Reviewer 1*		
1.0	Thank you for your clear response and modifications to the manuscript.	Thank you.	-
3	*Reviewer 3*		
3.0	This is a revised manuscript describing the protocol for a 2-arm RCT	Thank you.	-

	to evaluate the impact of LuCApp, a mobile supportive care app for patients with metastatic lung cancer on HRQoL, usability and resource utilization. The authors did a nice job addressing all the reviewers' comments. The manuscript is much improved by the revisions made.		
3.1	However, a minor sticky needs to be addressed. Page 11, description of intervention: line 54 "…research team will be in contact…". Is this ongoing contact (for troubleshooting and reminding) just for the purpose of this research or is this what would happen during implementation? This human resource effort would need to be accounted for in the cost/resource use analysis if not already planned. Also, to ensure that the study is replicable, please include the frequency of these calls as part of intervention procedures?	Thank you for pointing out lack of clarity at this point. The contact established by the research team is not expected to happen during full-scale implementation of the intervention but was deemed necessary for troubleshooting and reminding at this research stage. On average biweekly contacts are established with patients. The questionnaires administered to the clinicians to capture average per-patient time spent for LuCApp management will also cover this protocol-driven extra time spent on the app.	*Intervention* "…and, *for the purpose of this research only*, the research team will be in contact *approximately biweekly* by email or phone to verify if there are technical problems and to encourage app use." *Resource use* "Average per-patient clinician time spent for LuCApp management, *including troubleshooting or reminder contacts established with the patients*, or standard care management of lung cancer therapies' symptoms will be elicited with questionnaires administered to the clinicians at different time points during the study."