PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Impact of Mobile Applications on Adherence to Cancer Treatment: a Systematic Review and Meta-analysis Protocol
AUTHORS	Medeiros, Kleyton; Queiroz, Janice; Monteiro, Michelly; Costa, Weruska; Cobucci, Ricardo; Stransky, Beatriz; Gonçalves, Ana

VERSION 1 – REVIEW

REVIEWER	Jamie Jacobs Massachusetts General Hospital, USA
REVIEW RETURNED	22-Jan-2019

GENERAL COMMENTS	The manuscript titled, "The Impact of Mobile Applications on Adherence to Cancer Treatment: a Systematic Review Protocol," outlines the protocol to be used in conducting a systematic review of mobile applications for adherence to cancer treatment on the primary outcomes of adherence, with secondary outcomes. The protocol overall appears standard for a systematic review with a meta-analysis; however, there are some areas that authors could elaborate on and provide clarification. This reviewer has concerns about the ability to conduct a review on secondary outcomes. These are described below. Abstract: Strengths and limitations The abstract is a bit lengthy overall and could be more concise. It appears that the authors did not complete this section prior to submission, as it is in bullets rather than paragraph form. It was not clear until this point that the review aims to compare mobile app methods versus other methods. This should be clarified earlier on and included in the methods- which currently states that authors will search for studies that use mobile applications for adherence. Later in the manuscript, it seems that this is not the purpose of the review- please clarify the confusion for the reader. Introduction: Authors should expand on this section with details about why adherence is a problem (not just why oral therapy is preferred by patients) and what are the potential clinical implications of non-adherence. The mention of only education tools and reminder systems is concerning as behavior change theory would suggest that interventions only addressing education and reminders do not promote behavior change and do not sustain changes in behavior over the long-term. Interventions that address adherence behaviors may incorporate other theoretically-based skills, such as cognitive behavioral therapy and motivational interviewing. Authors should familiarize themselves with behavior change literature that is used to develop evidence-based interventions and

include this in the description of potential interventions that they may find in their search and include in the review.

Could authors provide more detail in the introduction about the literature of potential benefits of mobile applications and the applicability and research behind mhealth interventions that has prompted an increase in the development and use of mhealth interventions for oral treatment adherence?

The introduction would generally benefit from more rationale as to why this review is being conducted- what are the safety and adherence issues that mhealth interventions propose to address? Perhaps the authors could comment on the fact that many intervention components (e.g., education, reminders, CBT) have been tested and it is unclear which is most effective, the need to provide better clinical care for patients on oral antineoplastic agents and whether this review aims to address these questions…

Methods

Remain consistent with future tense throughout (researchers searched versus will search).

Can the authors be specific about their tests of treatment heterogeneity and what factors they will compare between treatments?

The primary outcome of adherence is justified. While quality of life is a likely secondary outcome for many of the trials that will be included in this review, there is concern about outcomes of "improvement in self-care" and "control of signs and symptoms." These are not common outcomes across studies and may be hard to compare across different interventions. May recommend just using adherence and quality of life as outcomes; however, this may depend on what the authors find when they actually conduct the review.

General:
Wording throughout the manuscript is somewhat colloquial. For example, consider "intervention mechanisms" rather than "How the intervention might work" for this section title.

Please have a native English speaker review the manuscript. Sentences such as "the outcome will be the better adherence to medication…" are grammatically incorrect. There are typographical and grammatical errors throughout the document that make it difficult to read and understand.

REVIEWER	Jennifer Jones
	UHN, CANADA
REVIEW RETURNED	08-Feb-2019

| GENERAL COMMENTS | This is a protocol paper for a systematic review and meta-analysis to examine the impact of mobile apps on adherence to oral chemotherapies. This is an important topic given the growing number of oral cancer therapies that rely on patient adherence. The manuscript requires additional details in the methods and clarification as well as editing for grammar and typos. I have tried to provide feedback to the authors which I hope is helpful.

Introduction: The rationale for this review is clear. It is not clear if the focus is on adjuvant chemotherapy only or also includes hormone therapy and other oral treatments that are emerging. On page 4 under "How the Intervention might work" the authors have not provided a good review of the literature on the theory around why these apps/interventions actually result in behavior change and improved long term adherence. They could also include some |

discussion on the intervention research that has been done to date in this field – not just mobile but in person as well as non-cancer. On the same page under "Why it is important…" the authors need to expand to provide the appropriate context and also check style. For example, the authors start this section with "It was established that the compliance rate for medication therapies was 40% to 50%.". The language is confusing and could be restated "Research has demonstrated that compliance rates for….". Also, information on what medication therapies they are referring to would be helpful. The literature on adherence to oral medications in general and in cancer treatments is rather sparse and the authors should use updated references and reviews. Ideally, they should include a review of the research on medication adherence in general, oral cancer therapies (there are some large studies and you need to look at adherence over time- especially with adjuvant hormone tx) and also include why this is important in terms of impact on survival. Also, in terms of the factors affecting adherence, patient beliefs is one of the most important factors which has not been included.

Objectives: based on stated objectives, it appears that the review will include adherence to all cancer treatment though this is not entirely clear throughout the paper and in the search strategy.
Methods:
-Patients: here it states that it is restricted to oral chemotherapies.
-Types of interventions: why restrict to only concurrent control group? I also expect that there will be few studies so the authors may consider expanding to other quasi-experimental designs. What if the mobile app is an electronic reminder? It is not clear what is to be included/excluded and why.
-Outcome: Adherence is primary which seems reasonable but is there any specific time point and adherence can be measured in several different ways. The secondary outcomes have not been justified from the literature review and seem somewhat unrelated and it is very unlikely there will be enough studies to include on these.
-Search Strategy: Consider working with a librarian to develop the search strategy using PICO.
-Selection of studies: This has been written as though the search has already been performed?
Under assessment of heterogeneity: The funnel plot is typically used to detect bias and small study effects.
-Analysis: Please expand on the analyses that will be conducted for the data synthesis.

REVIEWER	Marc Sae
	University of Girona, Spain
REVIEW RETURNED	03-Mar-2019

| GENERAL COMMENTS | In this protocol, the authors try to systematically review and perform a quantitative meta-analysis to determine the effect of mobile applications in the improvement of adherence to medication in cancer treatment. |
| | The authors have been very successful in achieving their objectives. The manuscript is very well structured. It is methodologically impeccable and contains all the elements that define a protocol. |

Reviewer: 1
Reviewer Name: Jamie Jacobs ~
Institution and Country: Massachusetts General Hospital, USA
Please state any competing interests or state 'None declared': None declared
Please leave your comments for the authors below
The manuscript titled, "The Impact of Mobile Applications on Adherence to Cancer Treatment: a Systematic Review Protocol," outlines the protocol to be used in conducting a systematic review of mobile applications for adherence to cancer treatment on the primary outcomes of adherence, with secondary outcomes. The protocol overall appears standard for a systematic review with a meta-analysis; however, there are some areas that authors could elaborate on and provide clarification. This reviewer has concerns about the ability to conduct a review on secondary outcomes. These are described below.

Abstract: Strengths and limitations
The abstract is a bit lengthy overall and could be more concise. It appears that the authors did not complete this section prior to submission, as it is in bullets rather than paragraph form. It was not clear until this point that the review aims to compare mobile app methods versus other methods. This should be clarified earlier on and included in the methods- which currently states that authors will search for studies that use mobile applications for adherence. Later in the manuscript, it seems that this is not the purpose of the review- please clarify the confusion for the reader.
R. We absolutely agree with the reviewer. These suggestions were followed. The abstract was shortened and substantially modified. The purpose of the review is to evaluate the effectiveness of mobile applications in the improvement of adherence. Other interventions such as: patient education, Reminder Tools, Calendars, pillboxes, Electronic Reminders, etc will not be evaluated.
Introduction:
Authors should expand on this section with details about why adherence is a problem (not just why oral therapy is preferred by patients) and what are the potential clinical implications of non-adherence. The mention of only education tools and reminder systems is concerning as behavior change theory would suggest that interventions only addressing education and reminders do not promote behavior change and do not sustain changes in behavior over the long-term. Interventions that address adherence behaviors may incorporate other theoretically-based skills, such as cognitive behavioral therapy and motivational interviewing. Authors should familiarize themselves with behavior change literature that is used to develop evidence-based interventions and include this in the description of potential interventions that they may find in their search and include in the review. Could authors provide more detail in the introduction about the literature of potential benefits of mobile applications and the applicability and research behind mhealth interventions that has prompted an increase in the development and use of mhealth interventions for oral treatment adherence?
The introduction would generally benefit from more rationale as to why this review is being conducted- what are the safety and adherence issues that mhealth interventions propose to address? Perhaps the authors could comment on the fact that many intervention components (e.g., education, reminders, CBT) have been tested and it is unclear which is most effective, the need to provide better clinical care for patients on oral antineoplastic agents and whether this review aims to address these questions…
R. All these suggestions were followed. The modifications are marked in red on the manuscript (Introduction section).

Methods

Remain consistent with future tense throughout (researchers searched versus will search).

R. This suggestion was followed (page 7, line 214)

Can the authors be specific about their tests of treatment heterogeneity and what factors they will compare between treatments?

R. The high heterogeneity predicted among the selected articles will occur due to the great diversity of protocols for the treatment of cancer and the variety of available mobile applications. The factors that will be compared are better Adherence and persistence with therapy, safety/toxicity, clinical disease-related outcomes, health care utilization, and patient engagement with some promising signs of improvement.

The high heterogeneity predicted among the selected articles will occur due to the great diversity of protocols for the treatment of cancer and the variety of available mobile applications. The factors that will be compared are better Adherence and persistence with therapy, safety/toxicity, clinical disease-related outcomes, health care utilization, and patient engagement with some promising signs of improvement. The heterogeneity of the studies will be evaluated in the funnel plot.As well as this, the heterogeneity between trial results will be evaluated using a standard X2 test with a significance level of p<0.1. To assess heterogeneity, we plan to compute the I2 statistic, which is a quantitative measurement of inconsistency across studies. A value of 0% indicates no observed heterogeneity, whereas I2 values of ≥50% indicate a substantial level of heterogeneity.

The primary outcome of adherence is justified. While quality of life is a likely secondary outcome for many of the trials that will be included in this review, there is concern about outcomes of "improvement in self-care" and "control of signs and symptoms." These are not common outcomes across studies and may be hard to compare across different interventions. May recommend just using adherence and quality of life as outcomes; however, this may depend on what the authors find when they actually conduct the review.

R. To obtain better scientific evidence, we have followed this important article:

Zerillo JA, Goldenberg BA, Kotecha RR, Tewari AK, Jacobson JO, KrzyzanowskaMK.Interventions to Improve Oral Chemotherapy Safety and Quality: A Systematic Review. JAMA Oncol. 2018 Jan 1;4(1):105-117. doi: 10.1001/jamaoncol.2017.0625.

Zerilloet al., (2017) found these significant outcomes: better adherence and persistence with therapy. the secondaries were safety/toxicity, clinical disease-related outcomes, health care utilization, and patient engagement with some promising signs of improvement.

General:

Wording throughout the manuscript is somewhat colloquial. For example, consider "intervention mechanisms" rather than "How the intervention might work" for this section title.

R. We can consider changing "How the intervention might work" to "Interventions mechanisms." However, in all the previous protocols published by the BMJ open was used "How the intervention might work." We followed these previously published articles.

Please have a native English speaker review the manuscript. Sentences such as "the outcome will be the better adherence to medication…" are grammatically incorrect. There are typographical and grammatical errors throughout the document that make it difficult to read and understand.

R. This suggestion was followed, and a native English speaker reviewed the manuscript.

Reviewer: 2
Reviewer Name: Jennifer Jones
Institution and Country: UHN, CANADA
Please state any competing interests or state 'None declared': None.

R. This suggestion was followed.

Please leave your comments for the authors below

This is a protocol paper for a systematic review and meta-analysis to examine the impact of mobile apps on adherence to oral chemotherapies. This is an important topic given the growing number of oral cancer therapies that rely on patient adherence. The manuscript requires additional details in the methods and clarification as well as editing for grammar and typos. I have tried to provide feedback to the authors which I hope is helpful.

R. We appreciate your attention to this matter.

Introduction: The rationale for this review is clear. It is not clear if the focus is on adjuvant chemotherapy only or also includes hormone therapy and other oral treatments that are emerging.

R We clarified this point on the manuscript. The purpose of this review/metanalysis is to evaluate the effectiveness of mobile applications in the improvement of adherence to oral chemotherapy and adjuvant hormonal therapy among cancer survivors.

On page 4 under "How the Intervention might work" the authors have not provided a good review of the literature on the theory around why these apps/interventions actually result in behavior change and improved long term adherence. They could also include some discussion on the intervention research that has been done to date in this field – not just mobile but in person as well as non-cancer. On the same page under "Why it is important…" the authors need to expand to provide the appropriate context and also check style. For example, the authors start this section with "It was established that the compliance rate for medication therapies was 40% to 50%.". The language is confusing and could be restated "Research has demonstrated that compliance rates for…." Also, information on what medication therapies they are referring to would be helpful. The literature on adherence to oral medications in general and in cancer treatments is rather sparse and the authors should use updated references and reviews. Ideally, they should include a review of the research on medication adherence in general, oral cancer therapies (there are some large studies and you need to look at adherence over time- especially with adjuvant hormone tx) and also include why this is important in terms of impact on survival. Also, in terms of the factors affecting adherence, patient beliefs isone of the most important factors which has not been included.

R. We agree with the reviewer. These suggestions were followed. The topics"How the Intervention might work" or "Intervention mechanisms" and "Why it is important to perform this review" were rewritten and substantially modified.

Objectives: based on stated objectives, it appears that the review will include adherence to all cancer treatment though this is not entirely clear throughout the paper and in the search strategy.

R. The purpose of this review is to evaluate the effectiveness of mobile applications in the improvement of adherence to oral chemotherapy and adjuvant hormonal therapy among" all types" of cancer survivors.

Methods:

-Patients: here it states that it is restricted to oral chemotherapies.

R. The review is restricted to oral hormonal and chemotherapies because in this situation the adherence is directly dependent on the patients.

-Types of interventions: why restrict to only concurrent control group? I also expect that there will be few studies so the authors may consider expanding to other quasi-experimental designs. What if the mobile app is an electronic reminder? It is not clear what is to be included/excluded and why.

R. The types of interventions will be directed related to the selected studies. Additionally, we can consider expanding to other quasi-experimental designs. Concerning the electronic reminder, they will be included, once they are a mobile app.

-Outcome: Adherence is primary which seems reasonable but is there any specific time point and adherence can be measured in several different ways. The secondary outcomes have not been justified from the literature review and seem somewhat unrelated and it is very unlikely there will be enough studies to include on these.
R. This point was clarified in the Methods section.

-Search Strategy: Consider working with a librarian to develop the search strategy using PICO.
R. A search strategy using PICO was developed and inserted in the manuscript.
-Selection of studies: This has been written as though the search has already been performed?
R. At first, the search strategy must be constructed before starting a systematic review.
Under assessment of heterogeneity: The funnel plot is typically used to detect bias and small study effects.
-Analysis: Please expand on the analyses that will be conducted for the data synthesis.
R. These suggestions are followed, and the modifications are marked in red on the manuscript (Methods section).

Reviewer: 3
Reviewer Name: Marc Saez
Institution and Country: University of Girona, Spain
Please state any competing interests or state 'None declared': None declared
R. This suggestion was followed.

Please leave your comments for the authors below In this protocol, the authors try to systematically review and perform a quantitative meta-analysis to determine the effect of mobile applications in the improvement of adherence to medication in cancer treatment.
The authors have been very successful in achieving their objectives. The manuscript is very well structured. It is methodologically impeccable and contains all the elements that define a protocol.

VERSION 2 – REVIEW

REVIEWER	Jennifer Jones UHN, CANADA
REVIEW RETURNED	26-Apr-2019

GENERAL COMMENTS	I commend the authors for trying to address the large number of comments provided by the reviewers. There remain some issues that need to be addressed. - If you are doing a meta-analysis, you need to add this to your title. Also suggest not putting review/metanalyses throughout but rather "systematic review and meta analysis" -in the Intervention mechanisms section, much of what has been added is confusing and disjointed, not properly referenced and needs to be edited for proper English. - the reference list has not been updated so the new references do not match. Suggest looking at some of the large studies of non-adherence in cancer populations which show non-adherence increases over time (i.e work by Hershman et al) -as mentioned in my previous review, health beliefs are very important to consider as they are the most important factor in predicting adherence along with side effect. - the authors have not addressed any of the previous comments by myself or reviewer 1 in terms of theory and why these apps may be helpful or not.

	-Has poor adherence to oral cancer medications been linked to increased hospitalizations or is this ref for other conditions? -under search strategy, given the authors state that apps were first developed in 2009, the search could start with that year. -suggest using a forest plot rather than a funnel plot when reporting outcomes -under types of interventions, again I am not sure why the authors are only considering parallel RCTs? Suggest including any studies where there was randomization and you may also want to expand to quasi-experimental designs. -Under Types of Outcome Measures- this section includes paragraphs which could be moved earlier and seem out of place. I am also not sure what "control of signs and symptoms" means. The third paragraph in this section is not clear. "Success in the therapy instituted by the physician and health team and economic benefits" . I think here you mean disease progression and relapse and in this case you would need studies which have followed patient long term which I do not expect you will find with RCTs.. I also don't understand the end of this sentence "in the assumption of social and professional roles". -The analyses section needs to be expanded. Consider a fixed effects model for the meta-analysis (except where statistical heterogeneity is identified and then use a random effects model) - The entire article needs to be proofed because there are several places where spaces are missing between words. Also, English language editing is still needed.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Jennifer JonesInstitution and Country: UHN, CANADA

1- If you are doing a meta-analysis, you need to add this to your title. Also suggest not putting review/metanalyses throughout but rather "systematic review and meta analysis"

R. Meta-analysis has been added in the title and methods.

2-in the Intervention mechanisms section, much of what has been added is confusing and disjointed, not properly referenced and needs to be edited for proper English.

- the reference list has not been updated so the new references do not match.

R. All the references were revised and updated. Additionally, the manuscript was totally revised by a native English speaker

3- Suggest looking at some of the large studies of non-adherence in cancer populations which show non-adherence increases over time (i.e work by Hershman et al)

R. This suggestion was followed, and this text was inserted in the manuscript:

Hershman et al. found that interventions to enhance the psychosocial well-being of patients should be evaluated to increase adherence. Furthermore, he explains in his study that adherence to therapy has been reported to be associated with belief in the efficacy of the medication and with belief in the benefits of taking prescribed medications more generally; and high levels of cancer-specific emotional distress were associated with subsequent non-persistence in treatment (7).

4 - As mentioned in my previous review, health beliefs are very important to consider as they are the most important factor in predicting adherence along with side effect.

R. We followed this recommendation and this text was inserted in the manuscript:

"Hershman et al. found that interventions to enhance the psychosocial well-being of patients should be evaluated to increase adherence. Furthermore, he explains in his study that adherence to therapy has been reported to be associated with belief in the efficacy of the medication and with belief in the benefits of taking prescribed medications more generally; and high levels of cancer-specific emotional distress were associated with subsequent non-persistence in treatment (7).

Another important finding is that the perception of poor physician–patient communication, negative beliefs regarding efficacy of the medication and fear of toxicities are associated with failure to initiate the therapy (6).

In a systematic review, Greer et al. (6) assessed interventions to improve adherence to oral antineoplastic therapies for patients with various malignancies. Interventions varied in format, and included educational support, treatment monitoring, pharmacy-based programs, counseling programs, prefilled pill boxes, and automated voice response systems. Nevertheless, most of these suffered high risk of bias due to nonrandomized designs, small sample sizes, subjective assessments of adherence, and missing data concerns. In another systematic review of interventions to promote adherence to oral antineoplastic therapies that has been published to date, the investigators drew similar conclusions (8)."

5 - The authors have not addressed any of the previous comments by myself or reviewer 1 in terms of theory and why these apps may be helpful or not.

R. The advantages of mobile applications (MA) over other interventions are simplicity and ease of administration, often in an automated fashion using a computerized program (6). Thus, MA may be useful for promoting healthy behaviors and lifestyles, while monitoring, tracking, collecting and transmitting data in real time, facilitating the doctor-patient communication, and increasing the level of sharing and cooperation between the patient and health professionals (7).

Several techniques may increase adherence to treatment. However, most effective interventions include behavioral approaches and there is no consensus on which behavioral techniques (e.g., specific goal setting, self-monitoring, and social comparison) are central to effective medication adherence interventions (7).

With the ever-growing presence of smartphones and the potential for efficacious behavioral intervention technology, scientists may implement momentary interventions and momentary assessments in order to collect data in real-time in real and convenient real-world situations. Along with this, researchers are thus able to optimize the delivery of behavioral interventions and collect ongoing data with minimal burden to the patient and provider (11). A recent review indicates that adopting mobile technologies to deliver accessible interventions can improve health behaviors in patients with cancer (13)."

6 -Has poor adherence to oral cancer medications been linked to increased hospitalizations or is this ref for other conditions?

R. We followed this recommendation, and the text above was inserted in this manuscript

"As a consequence of the absence of the correct intake of doses of oral medication by the cancer patient, there may be additional treatment costs due to the increased frequency of hospitalization and return to medical appointments, reappearance of symptoms, and consequent increase in drug toxicity due to overdosage (to make up for the missed dose) (4, 22-25).

The primary outcome will be the improved adherence to medication in cancer treatment (17). The secondary outcomes will be an improvement in overall survival and life expectancy, improved quality of life and control of symptoms related to cancer (9-11)."

7 - under search strategy, given the authors state that apps were first developed in 2009, the search could start with that year.

R. This suggestion was followed, the search strategy started in 2009.

8 - suggest using a forest plot rather than a funnel plot when reporting outcomes

R. This advice was followed

9 - under types of interventions, again I am not sure why the authors are only considering parallel RCTs? Suggest including any studies where there was randomization and you may also want to expand to quasi-experimental designs.

R. This suggestion was followed by including any studies where there was randomization

10 -Under Types of Outcome Measures- this section includes paragraphs which could be moved earlier and seem out of place. I am also not sure what "control of signs and symptoms" means. The third paragraph in this section is not clear. "Success in the therapy instituted by the physician and health team and economic benefits" . I think here you mean disease progression and relapse and in this case you would need studies which have followed patient long term which I do not expect you will find with RCTs.. I also don't understand the end of this sentence "in the assumption of social and professional roles".

R. These recommendations were followed, and this text was inserted in the manuscript

"As a consequence of the absence of the correct intake of doses of oral medication by the cancer patient, there may be additional treatment costs due to the increased frequency of hospitalization and return to medical appointments, reappearance of symptoms, and consequent increase in drug toxicity due to overdosage (to make up for the missed dose) (4, 22-25).

The primary outcome will be the improved adherence to medication in cancer treatment (17). The secondary outcomes will be an improvement in overall survival and life expectancy, improved quality of life and control of symptoms related to cancer (9-11)."

11-The analyses section needs to be expanded. Consider a fixed effects model for the meta-analysis (except where statistical heterogeneity is identified and then use a random effects model)

R. We followed this suggestion and the analyses section was expanded. Additionally, a fixed effects model for the meta-analysis was considered.

12- The entire article needs to be proofed because there are several places where spaces are missing between words. Also, English language editing is still needed.

R: The manuscript was totally revised by a native English speaker (The certification was submitted as a file).