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The Impact of Mobile Applications on Adherence to Cancer Treatment: a Systematic Review Protocol

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Keywords:	mobile application, medication adherence, oral anticancer agents, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, patient compliance

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The Impact of Mobile Applications on Adherence to Cancer Treatment: a Systematic Review Protocol

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Conflict of Interest statement: None

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ABSTRACT

Introduction

About 25% of new antineoplastic agents in development are estimated to be oral drugs. Once an antineoplastic agent is ordered, the administration is the responsibility of the patient and this has created significant safety and adherence issues. To overcome these difficulties, oncology nurses can use tools and technology to assist with education, which may promote adherence with the suggestion of reminder tools that can be used. This review aims to assess the efficacy of mobile applications to improve the adherence to medication in cancer treatment.

Methods and analysis

The databases MEDLINE, Embase, SciELO, Scopus and Cochrane Database of Systematic Reviews will be used to search for articles from January 2018. Clinical Trials, Controlled Clinical Trials, Randomized Controlled Trials using mobile applications in patients to aid adherence to medication in cancer treatment will be included. The primary outcome will be the better adherence to medication in cancer treatment. The secondary outcome will be Improvement in Self-care, improved quality of life and control of signs and symptoms. Three independent reviewers will select trials and extract data from the original publications. The risk of bias will be assessed according to the Cochrane Risk of Bias tool. Data synthesis will be performed using Review Manager software (RevMan V.5.2.3). To assess heterogeneity, we will compute the I2 statistic. The heterogeneity of the studies will be evaluated in the funnel plot. Additionally, a quantitative synthesis will be used if the included studies are sufficiently homogenous.

Ethics and dissemination

This study will be a review of the published data and thus it is not necessary to obtain ethical approval. Findings of this systematic review will be published in a peer-reviewed journal.

Trial registration number

International Prospective Register of Systematic Reviews 2018: CRD42018102172.

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Strengths and limitations of this study

- The results obtained from this systematic review will propose which strategy is most useful for the improvement of adherence to oral chemotherapeutic treatment, choosing between mobile app and others methods.
- Two reviewers will independently select the eligibility trials to be included in this review, extract data without different variables and assess the risk of bias
- Our review and meta-analysis aims to combine the results of different studies that have comparable effect sizes that can be computed. However, it may be that we will only get a small sample size and a limited number of studies, which may influence the validity and reliability of the findings.
- Our review would be limited by variation of strategies for adherence to oral chemotherapy and quality of the randomized trials used in the systematic review.

Introduction

Description of the condition

About 25% of new antineoplastic agents in development are estimated to be oral drugs, and the number of available oral chemotherapy medications is expected to more than double over the next few years (1-3). Oral therapy is often preferred by patients to IV therapy for several reasons. The benefits of oral agents for cancer are: patient preference, convenience of use, easier administration and more convenience for patients because they result in fewer office visits and less time spent receiving treatment compared to IV chemotherapy (4,5). Additionally, oral therapy can provide a feeling of control over treatment, decrease treatment interference with work and social activities, eliminating the travel time needed to go to an infusion clinic, and eliminate the discomfort of having an IV line inserted for each administration (2). Once an antineoplastic agent is ordered, the administration is the responsibility of the patient (5). However, the problem of non-adherence to treatment and pharmacological limitations are still poorly studied (3).

Description of the intervention

Oncology nurses can use tools and technology to assist with education, which may promote adherence with the suggestion of reminder tools that can be used.

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Many have already been developed: patient education; physical devices such as pillboxes and glowing pill bottles; or computer and mobile applications (apps) to work as electronic reminders, such as calendars, text messaging, and alarms (5). This article aims to verify if the use of mobile applications improves the patient in adherence to medication in cancer treatment.

How the intervention might work

Mobile applications are computer programs or software installed on mobile electronic devices which support a wide range of functions and uses which include television, telephone, video, music, word processing, and Internet service (6). Based on the researchers' analysis of available apps, medication reminder apps were first developed in 2009 (5). For the purpose of this study, the mobile application will replicate (or show, inform) the medical and nursing orientations for use of oral chemotherapy drugs at home, i.e., how to take, the principle reactions, and principle interactions. Additionally, they will remind the patient to take the medication at the right time and right dose as prescribed (7).

Why it is important to perform this review

It was estimated that the compliance rate for long-term medication therapies was 40% to 50%. The rate of compliance for short-term therapy was much higher at 70% to 80%, while the compliance with lifestyle changes was the lowest, at 20% to 30% (8). Presently, the average rate of non-adherence to oral anti-cancer therapy is estimated to be around 21% (4), that is, poor adherence is a barrier to completing the treatment (9,10). Non-adherence is complex and systemic, as well as this, at home there is no professional oversight to know whether patients are properly taking the medication as prescribed. Oral regimens may come with complicated dosing schedules or multiple food and drug interactions that make adherence difficult. In busy clinics, patients may be given written materials about the new medication, but little time may be available for one-on-one interaction (5). Ensuring patient adherence to a treatment that involves self-administration is a challenge that is faced by health care providers (2,11). Many factors can affect the treatment adherence: lack of understanding regarding proper administration, complex dosing regimens, administration of other potentially interacting medications, timing of treatment

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doses in relation to food intake, cost of the drug, and unpleasant side effects. Furthermore, common health conditions of the patients such as visual and cognitive impairment, memory deficits or forgetfulness can pose another difficulties (2). In this context, it is necessary to verify if the use of mobile applications can help the patient to overcome those difficulties and improve the adherence to treatment. Despite the increased use of oral chemotherapy, the number of studies addressing the issue of adherence remains surprisingly low (11).

Objectives

The objective of the study is to systematically review and, if possible, perform a quantitative meta-analysis to determine the effect of mobile applications in the improvement of adherence to medication in cancer treatment.

Materials and methods

This protocol is registered with the International Prospective Register of Systematic Reviews, registration number CRD42018102172. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (12) statement guidelines were used to construct this systematic review protocol. International Prospective Register of Systematic Reviews 2018: CRD42018102172.

Types of studies

This review will include studies that fall in these criteria: (a) Clinical Trial, Controlled Clinical Trial or Randomized Controlled Trial, (b) studies including adult subjects (18 years of age); (c) studies published up to January 2018; (d) studies including adherence to cancer treatment with oral medications and use of mobile applications; (e) clinical trials evaluating the use of mobile applications for adherence to oral treatment in cancer patients and (f) no language restrictions.

Types of patients

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Participants of the studies are adults (older than 18 years) diagnosed with cancer, using ongoing oral chemotherapy medications and using mobile applications to improve their adherence to medication.

Types of interventions

Parallel Randomized Controlled Trials (RCTs) that compare the use of the mobile application with a concurrent control group, which does not use the mobile application. Other interventions will not be evaluated, for example: patient education, Reminder Tools, Calendars, pillboxes, Electronic Reminders, etc. (9,10).

Types of outcome measures

The primary outcome will be the improved adherence to medication in cancer treatment. The secondary outcome will be improvement in self-care, better life quality and control of signs and symptoms. Another outcome is the success of the therapy instituted by the physician and health team and economic benefits (reduction of exacerbation of the disease, crisis or relapse); in the assumption of social and professional roles (13). Consequences of non-adherence are not only an increase in consumption resources from the health system, such as the number of medical consultations and emergency consultations, more frequent hospitalizations with longer duration, but also an increase in treatment toxicity, bias in the evaluation of drug efficacy and an increase in mortality (4, 14-15).

Search methods for identification of studies

Electronic searches

The databases MEDLINE, Embase, SciELO, Scopus and Cochrane Database of Systematic Reviews will be used to search for articles. No language restrictions will be used, no restrictions on publication period will be applied. The descriptor terms will be: (antineoplastic agents OR oral anticancer agents OR drug therapy) AND (mobile application OR mobile apps OR app OR smartphone OR health informatics OR mobile health) AND (medication adherence OR patient empowerment OR treatment adherence and compliance).

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Other sources

The scope of the computerized literature search will be enlarged on the basis of the reference lists of retrieved articles.

Patient and Public Involvement

The research will be performed by a wide and comprehensive search of literature from data bases and the individual patient data are not included. Thus, the authors no involved patients in setting there search question, as well as, the outcome measures, the design and implementation of the study, and the dissemination of its results.

Search strategy

Table 1 presents the search strategy for Medline.

Table 1 Medline search strategy

Search items	
1	antineoplastic agents
2	oral anticancer agents
3	drug therapy
4	Or/1-3
5	mobile application
6	mobile apps
7	smartphone
8	health informatics
9	mobile health
10	Or/5-9
11	medication adherence
12	patient participation
13	patient compliance
14	treatment adherence and compliance
15	MedicationTherapy Management
16	Or/11-15
17	4 and 10 and 16

Data collection and analysis

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Selection of studies and Search and selection of literature

The articles published up to January 2018 were identified by a wide literature search of databases following the terms of the medical subject headings and/or text words: (antineoplastic agents OR oral anticancer agents OR drug therapy) AND (mobile application OR mobile apps OR app OR smartphone OR health informatics OR mobile health) AND (medication adherence OR patient empowerment). Moreover, the bibliographies of the reviewed articles were included. Three researchers (KSM, WAC, and JFQ) searched for articles published up to January 2018

Study identification and selection is illustrated in the flow diagram in Fig. 1. After searching the databases, potentially relevant papers will beidentified and the others excluded after reviewing the title or after reviewing the abstract. Reviews will be made by KSM, WAC, and JFQ; disagreements will be solved by a fourth reviewer (AKSG). Thus, papers that meet the criteria will be reviewed in full. After the full review, papers that are considered to not have adequate methodological quality according to the GRADE guidelines will be excluded. Finally, repeated studies that are found (being present in two databases at the same time) will be excluded. Finally, papers will be approved for data extraction (Fig. 1).

Insert **Figure 1:** Flow diagram of the search for eligible studies in the use of mobile applications for adherence to cancer treatment: CENTRAL, Cochrane Central Register of Controlled Trials.

Data extraction and management

Various study characteristics will be extracted from the original research and included in the systematic review. The data to be included are the first authors' last names, year of publication, location of the study (country), study design, primary objective, population, sample size, follow-up period, inclusion/exclusion criteria, type of App used, type of control used, and primary results. Standardized data extraction forms will specifically be created for this review and the results will be subsequently entered into a database. All data entry will be double-checked. Three blind reviewers (KSM, WAC, and JFQ) use the

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inclusion criteria to choose available articles. Disagreements will be solved by means of mutual consensus.

Risk of bias assessment

Three review authors will independently assess the risk of bias in the included studies using the Cochrane risk of bias tool. The modified Cochrane Collaboration tool will be used to assess risk of bias for randomized controlled trials. Bias is assessed as a judgment (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other) (16).

Assessment of heterogeneity

The bias of publication will be mitigated with a comprehensive, sensitive, unrestricted search for language and with an extensive search in the gray literature.

The heterogeneity of the studies will be evaluated in the funnel plot. Additionally, a quantitative synthesis will be used if the included studies are sufficiently homogenous.

As well as this, the heterogeneity between trial results will be evaluated using a standard X^2 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 I^2 values of ≥50% indicate a substantial level of heterogeneity.

Analysis

Data will be entered in the Review Manager software (RevMan5.2). This software allows the user to enter protocols, to complete reviews, include text, characteristics of the studies, comparison tables and study data, and to perform meta-analyses of the data that the Odds Ratios will obtain.

DISCUSSION

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The adherence to cancer treatment is a very common and relevant clinical problem, with a significant adverse impact on the health system. In this review, we aim to determine the effect of mobile applications in the improvement of adherence to medication in cancer treatment. In theory, mobile applications can improve adherence to cancer treatment, because it reminds the patient of the time to take the medicine and assists in the management of care. Therefore, mobile phone applications (apps), may support oncology patients with medication and disease management (17). We expect that our review will provide accurate data for effective strategies for adherence to cancer treatment. Furthermore, this review will improve our understanding of adherence to cancer treatment with mobile applications.

Ethics and dissemination

Ethical approval is not required because this systematic review will use published patient data. Findings of this systematic review will be published in a peer-reviewed journal and updates will be conducted if there is enough new evidence that may cause any change in the review conclusions.

REFERENCES

1. Weingart SN, Flug J, Brouillard D, et al. Oral chemotherapysafetypracticesat US cancer centres: questionnairesurvey. BMJ. 2007; 334:407-10.

2. Wood L. A review onadherence management in patientson oral cancertherapies. Eur J OncolNurs 2012;16:432–8.

3. Moody M, Jackowski J. Are patientson oral chemotherapy in yourpractice setting safe?Clin J OncolNurs. 2010, 14: 339-346.

4. Chabrier M, Bezy O, Mouret MA, Bay JO, Jalenques I. Impact of depressive disorders on adherence to oral anti-cancer treatment. Bulletin Du Cancer. 2013; 10: 1017-1022.

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5. Burhenn, P.S.; Smudde, J. Using tools andtechnologytopromoteeducationandadherenceto oral agents for cancer. Clin. J. Oncol. Nurs. 2015, 19, 53–59.

6. MEDICINE, U.S. National Library Of MEDICINE. Medical Subject Headings: Mobile Applications. 2018. Disponível em: <https://www.ncbi.nlm.nih.gov/mesh/68063731>. Acesso em: 06 out. 2018.

7. Elliott M, Liu Y. The nine rightsofmedicationadministration: an overview. Br J Nurs. 2010;19(5):300-5.

8. DiMatteo MR. Patientadherencetopharmacotherapy: theimportanceofeffective communication. Formulary. 1995;30:596–8. 601–2, 605.

9. Makubi A, Sasi P, Ngaeje M, et al. Rationaleand design ofmDOT-HuAstudy: a randomizedtrialtoassesstheeffectof mobile-directlyobservedtherapyonadherencetohydroxyurea in adultswithsicklecell anemia in Tanzania. BMC Med Res Methodol. 2016;16(1):140.

10. Thakkar J, Kurup R, Laba, T, et al. Mobile TelephoneTextMessaging for MedicationAdherence in ChronicDisease: A Meta-analysis. JAMA Internal Medicine. 2016:176(3):340-349.

11. Barillet M, Prevost V, Joly F, Clarisse B. Oral antineoplasticagents: How do wecareaboutadherence? Br J ClinPharmacol2015;80:1289-302.

12. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA GroupPreferredreportingitems for systematic reviews and meta-analyses: The PRISMA StatementPLoSMed, 6 (2008), p. e1000097. doi: 10.1371/journal.pmed.1000097

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13. Shimada CS. Adherence to treatment with oral medications. Rio de Janeiro: Elsevier, 2016.

14. RuddyK,Mayer E, PartridgeA. Patientadherenceandpersistencewith oral anticancertreatment. CA Cancer J Clin2009;59:56–66.

15. Jingjin, Grant ES , Vernon MS Oh, Shuchuen li. Factorsaffectingtherapeuticcompliance: A review fromthepatient's perspective. TherClin Risk Manag. 2008; 4(1): 269-286.

16. Higgins, PTJ, Altman, DG, Gotzsche, PC, Juni, P, Moher, D, Oxman, AD, et al. The Cochrane Collaboration's tool for assessingriskof bias in randomisedtrials. BMJ. 2011; 343, d5928.

17. Jupp JCY, Sultani H, Cooper CA, Peterson KA, Truong TH. Evaluationof mobile phoneapplicationstosupportmedicationadherenceandsymptom management in oncologypatients. PediatricBlood&Cancer. 2018;65(11):e27278.

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Contributors KSM, BS and AKG contributed to the design of this review. KSM drafted the protocol manuscript, and AKG revised it. KSM, RNC and AKG developed the search strategies and KSD, JFQ and AS will implement them. KSM, AS, JFQ, and WAC will track potential studies, extract data and assess quality. In case of disagreement between the data extractors, AKG will advise on the methodology and will work as the referee. RNC will complete the data synthesis. All authors have approved the final version for publication.

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Competing interests None declared.

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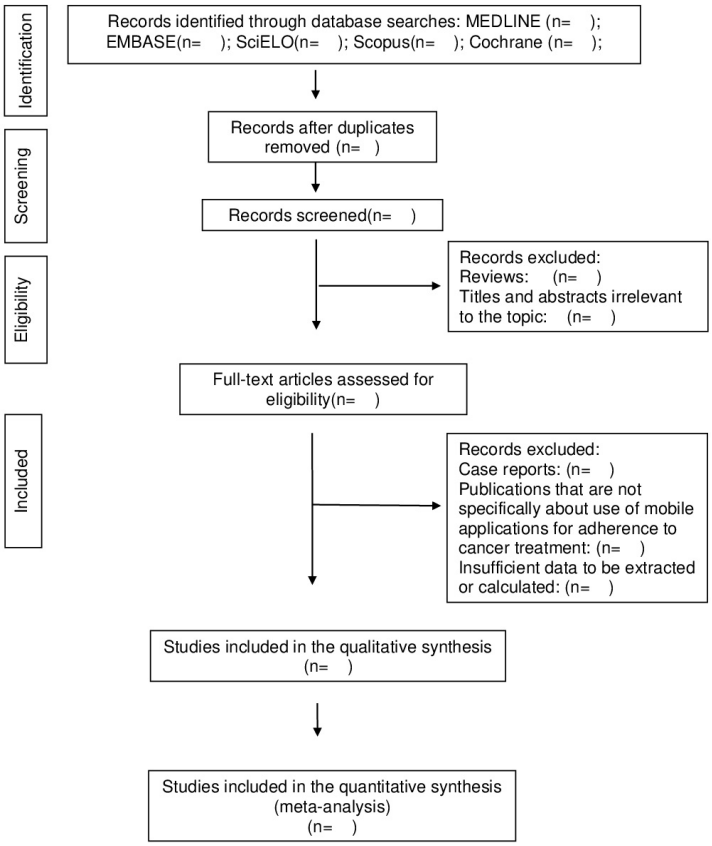

Figure 1 Flow diagram of the search for eligible studies in the use of mobile applications for adherence to cancer treatment: CENTRAL, Cochrane Central Register of Controlled Trials.

419x594mm (72 x 72 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	X
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	X
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	X
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	X
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	X
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	X
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	X
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	X
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	X
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	X
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	X
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	X
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	X
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	X
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	X
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	X
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	X

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Communication, Nursing
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Conflict of Interest statement: None

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ABSTRACT

Introduction

The number of patients taking oral chemotherapy is Increasing around the world; this is essential to maximize adherence to oral chemotherapy to improve overall survival and life expectancy. This review aims to evaluate the effectiveness of mobile applications in the improvement of adherence to oral chemotherapy and adjuvant hormonal therapy among cancer survivors.

Methods and analysis

The databases MEDLINE, Embase, SciELO, Scopus and Cochrane Database of Systematic Reviews will be used to search for articles from January 2018. Clinical Trials, Controlled Clinical Trials, Randomized Controlled Trials using mobile applications among cancer survivors to aid adherence to oral chemotherapy and adjuvant hormonal therapy.Other interventions such as: patient education, Reminder Tools, Calendars, pillboxes, Electronic Reminders, etc will not be evaluated.The primary outcome will be better Adherence and/or persistence with therapy. The secondary outcome will be safety/toxicity, clinical disease related outcomes, health care utilization, and patient engagement with some promising signs of improvement. Three independent reviewers will select trials and extract data from the original publications. The risk of bias will be assessed according to the Cochrane Risk of Bias tool. Data synthesis will be performed using the Review Manager software (RevMan V.5.2.3). To assess heterogeneity, we will compute the I2 statistic. The heterogeneity of the studies will be evaluated in the funnel plot. Additionally, a quantitative synthesis will be used if the included studies are sufficiently homogenous.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- This review/meta-analysis aims to combine the results of different studies that have comparable effect sizes that can be computed.
- Three reviewers will independently select the eligibility trials to be included in this review, extract data without different variables and assess the risk of bias.
- However, it may be that we will only get a small sample size and a limited number of studies, which may influence the validity and reliability of the findings.
- Additionally, different types of mobile app may cause considerable heterogeneity that might be deficient in generating convincing conclusions.
- Despite these limitations, the results obtained from this systematic review will propose which strategy is most useful for the improvement of adherence to oral chemotherapeutic treatment, choosing between the mobile app and other approaches.

INTRODUCTION

Description of the condition

About 25% of new antineoplastic agents in development are estimated to be oral drugs, and the number of available oral chemotherapy medications is expected to more than double over the next few years (1-3). Oral therapy is often preferred by patients to IV therapy for several reasons. The benefits of oral agents for cancer are: patient preference, convenience of use, easier administration and more convenience for patients because they result in fewer office visits and less time spent receiving treatment compared to IV chemotherapy (4,5). Additionally, oral therapy can provide a feeling of control over treatment, decrease treatment interference with work and social activities, eliminating the travel time needed to go to an infusion clinic, and eliminate the discomfort of having an IV line inserted for each administration (2). Once an antineoplastic agent is ordered, the administration is the responsibility of the patient (5). However, the problem of non-adherence to treatment and pharmacological limitations are still poorly studied (3).

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Mobile applications are computer programs or software installed on mobile electronic devices which support a wide range of functions and uses which include television, telephone, video, music, word processing, and Internet service (6). Based on the researchers' analysis of available apps, medication reminder apps were first developed in 2009 (5). For the purpose of this study, the mobile application will replicate (or show, inform) the medical and nursing orientations for use of oral chemotherapy drugs at home, i.e., how to take, the principle reactions, and principle interactions. Additionally, they will remind the patient to take the medication at the right time and right dose as prescribed (7).

In the treatment of chronic diseases, adherence to treatment remain a complicated issue. (8-10). In these situations, It is recognized the benefit of interventions, even if it is a simple intervention (text message). (10). These interferences increase medication adherence, with a doubling of the odds of patients' achieving adherence to their medication regimens. The latter increase adherence rates from 50% to 67.8%.

The advantages of mobile applications over other interventions are simplicity and ease of administration, often in an automated fashion using a computerized program.

Mobile applications may be useful for promoting healthy behaviors and lifestyles, monitor, track, collect and transmit data in real time, facilitating the doctor-patient communication, increasing the level of sharing and cooperation between the patient and health professionals.

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Several techniques may increase adherence to treatment. The most effective interventions include behavioral approaches; however, 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.

Why it is important to perform this review

Traditional interventions to improve adherence are complex and not widely useful. All interventions effective for long-term care were involved and not widely useful. There is a widespread need for convenient and feasible innovations to help patients remain adherent to medications (10).

Presently, the average rate of non-adherence to oral anti-cancer therapy is estimated to be around 21% (4); that is, poor adherence is a barrier to completing the treatment (9,10). Non-adherence is complex and systemic, as well as this, at home there is no professional oversight to know whether patients are correctly taking the medication as prescribed. Oral regimens may come with complicated dosing schedules or various foods and drug interactions that make adherence difficult. In busy clinics, patients may be given written materials about the new medication, but little time may be available for one-on-one interaction (5). Ensuring patient adherence to a treatment that involves self-administration is a challenge that is faced by health care providers (2,11). Many factors can affect the treatment adherence: lack of understanding regarding proper administration, complex dosing regimens, administration of other potentially interacting medications, the timing of treatment doses concerning food intake, cost of the drug, and unpleasant side effects. Furthermore, common health conditions of the patients such as visual and cognitive impairment, memory deficits or forgetfulness can pose other difficulties (2).

Poor adherence has been linked to successive hospitalizations, increased need for medical interventions, morbidity, and mortality. Besides, medication non-adherence results increased health care cost, with estimates from North America of approximately $100 billion being spent annually and $2000 spent per patient per year in excess physician visits (10).

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In this context, it is necessary to verify if the use of mobile applications can help the patient to overcome those difficulties and improve the adherence to treatment. Despite the increased use of oral chemotherapy, the number of studies addressing the issue of adherence remains surprisingly low (11).

Objectives

This review/metanalysis aims to evaluate the effectiveness of mobile applications in the improvement of adherence to oral chemotherapy and adjuvant hormonal therapy among cancer survivors.

Materials and methods

This protocol is registered with the International Prospective Register of Systematic Reviews, registration number CRD42018102172. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (12) statement guidelines were used to construct this systematic review protocol. International Prospective Register of Systematic Reviews 2018: CRD42018102172.

Types of studies

This review will include studies that fall in these criteria: (a) Clinical Trial, Controlled Clinical Trial or Randomized Controlled Trial, (b) studies including adult subjects (18 years of age); (c) studies published up to July2019; (d) studies including adherence to cancer treatment with oral medications and use of mobile applications; (e) clinical trials evaluating the use of mobile applications for adherence to oral chemotherapy and adjuvant hormonal therapy among cancer survivors (f) no language restrictions.

The PICO strategy

- Population/Participants: Patients on oncological treatment with oral chemotherapy and adjuvant hormonal therapy among cancer survivors
- Intervention: Use of mobile application
- Comparator/control: Do not use mobile application
- Outcome: Improvement adherence to medication in cancer treatment.

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Types of patients

Participants of the studies are adults (older than 18 years) diagnosed with cancer, using ongoing oral chemotherapy and adjuvant hormonal therapy, using mobile applications to improve their adherence to medication.

Types of interventions

Parallel Randomized Controlled Trials (RCTs) that compare the use of the mobile application with a concurrent control group, which does not use the mobile application. Other interventions will not be evaluated, for example: patient education, Reminder Tools, Calendars, pillboxes, Electronic Reminders, etc (9,10).

Types of outcome measures

Various methods of adherence were reported in the literature including self-report, medication measurement, patient report/survey, Morisky-green Test, pill count, electronic cap monitoring, and pharmacy fill data or combinations of methods. Each method has advantages and limits, and a gold standard still does not exist. (8).

The primary outcome will be the improved adherence to medication in cancer treatment. (8). The secondary outcomes will be an improvement in overall survival and life expectancy, improved quality of life and control of signs and symptoms. Patients risk improper dosing and an increase in disease recurrence when there is nonadherence with medications; then the safety/toxicity profile was the secondary outcome. (8).

Another outcome will be the success of the therapy instituted by the physician and health team and economic benefits (reduction of exacerbation of the disease, crisis or relapse); in the assumption of social and professional roles (13).

Consequences of non-adherence are not only an increase in consumption resources from the health system, such as the number of medical consultations and emergency consultations, more frequent hospitalizations with longer

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duration but also an increase in treatment toxicity, bias in the evaluation of drug efficacy and an increase in mortality (4, 14-15).

Search methods for identification of studies

Electronic searches

The databases MEDLINE, Embase, SciELO, Scopus and Cochrane Database of Systematic Reviews will be used to search for articles. No language restrictions will be used, no restrictions on publication period will be applied. The descriptor terms will be: (antineoplastic agents OR oral anticancer agents OR drug therapy) AND (mobile application OR mobile apps OR app OR smartphone OR health informatics OR mobile health) AND (medication adherence OR patient empowerment OR treatment adherence and compliance).

Other sources

The scope of the computerized literature search will be enlarged on the basis of the reference lists of retrieved articles.

Patient and Public Involvement

The research will be performed by a wide and comprehensive search of literature from data bases and the individual patient data are notincluded. Thus, the authors no involved patients in setting there search question, as well as, the outcome measures, the design and implementation of the study, and the dissemination of its results.

Search strategy

Table 1 presents the search strategy for Medline.

Table 1 Medline search strategy

Search items	
1	antineoplastic agents
2	oral anticancer agents
3	drug therapy
4	Or/1-3

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5	mobile application
6	mobile apps
7	Smartphone
8	health informatics
9	mobile health
10	Or/5-9
11	medication adherence
12	patient participation
13	patient compliance
14	treatment adherence and compliance
15	MedicationTherapy Management
16	Or/11-15
17	4 and 10 and 16

Data collection and analysis

Selection of studies and Search and selection of literature

The articles published up to July 2019will be identified by a wide literature search of databases following the terms of the medical subject headings and/or text words: (antineoplastic agents OR oral anticancer agents OR drug therapy) AND (mobile application OR mobile apps OR app OR smartphone OR health informatics OR mobile health) AND (medication adherence OR patient empowerment). Moreover, the bibliographies of the reviewed articles were included. Three researchers (KSM, WAC, and JFQ) searched for articles published up to January 2018

Study identification and selection is illustrated in the flow diagram in Fig. 1. After searching the databases, potentially relevant papers will beidentified and the others excluded after reviewing the title or after reviewing the abstract. Reviews will be made by KSM, WAC, and JFQ; disagreements will be solved by a fourth reviewer (AKSG). Thus, papers that meet the criteria will be reviewed in full. After the full review, papers that are considered to not have adequate methodological quality according to the GRADE guidelines will be excluded. Finally, repeated studies that are found (being present in two databases at the

same time) will be excluded. Finally, papers will be approved for data extraction (Fig. 1).

Insert **Figure 1:** Flow diagram of the search for eligible studies in the use of mobile applications for adherence to cancer treatment: CENTRAL, Cochrane Central Register of Controlled Trials.

Data extraction and management

Various study characteristics will be extracted from the original research and included in the systematic review. The data to be included are the first authors' last names, year of publication, location of the study (country), study design, primary objective, population, sample size, follow-up period, inclusion/exclusion criteria, type of App used, type of control used, and primary results. Standardized data extraction forms will specifically be created for this review and the results will be subsequently entered into a database. All data entry will be double-checked. Three blind reviewers (KSM, WAC, and JFQ) use the inclusion criteria to choose available articles. Disagreements will be solved by means of mutual consensus.

Risk of bias assessment

Three review authors will independently assess the risk of bias in the included studies using the Cochrane risk of bias tool. The modified Cochrane Collaboration tool will be used to assess risk of bias for randomized controlled trials. Bias is assessed as a judgment (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other) (16).

Assessment of heterogeneity

The bias of publication will be mitigated with a comprehensive, sensitive, unrestricted search for language and with an extensive search in the gray literature.

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

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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. Additionally, a quantitative synthesis will be used if the included studies are sufficiently homogenous.

As well as this, the heterogeneity between trial results will be evaluated using a standard X^2 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 I^2 values of ≥50% indicate a substantial level of heterogeneity.

Analysis

Data will be entered in the Review Manager software (RevMan5.2). This software allows the user to enter protocols, to complete reviews, include text, characteristics of the studies, comparison tables and study data, and to perform meta-analyses of the data that the Odds Ratios will obtain.

DISCUSSION

The adherence to cancer treatment is a very common and relevant clinical problem, with a significant adverse impact on the health system. In this review, we aim to determine the effect of mobile applications in the improvement of adherence to medication in cancer treatment. In theory, mobile applications can improve adherence to cancer treatment, because it reminds the patient of the time to take the medicine and assists in the management of care. Therefore, mobile phone applications (apps), may support oncology patients with medication and disease management (17,18). We expect that our review will provide accurate data for effective strategies for adherence to cancer treatment. Furthermore, this review will improve our understanding of adherence to cancer treatment with mobile applications.

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Ethics and dissemination

Ethical approval is not required because this systematic review will use published patient data. Findings of this systematic review will be published in a peer-reviewed journal and updates will be conducted if there is enough new evidence that may cause any change in the review conclusions.

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Contributors KSM, BS and AKG contributed to the design of this review. KSM drafted the protocol manuscript, and AKG revised it. KSM, RNC and AKG developed the search strategies and KSD, JFQ and AS will implement them. KSM, AS, JFQ, and WAC will track potential studies, extract data and assess quality. In case of disagreement between the data extractors, AKG will advise on the methodology and will work as the referee. RNC will complete the data synthesis. All authors have approved the final version for publication.

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REFERENCES

1. Weingart SN, Flug J, Brouillard D, et al. Oral chemotherapysafetypracticesat US cancer centers: questionnaire survey. BMJ. 2007; 334:407-10.
2. Wood L. A review onadherence management in patientson oral cancertherapies. Eur J Oncol Nurs 2012;16:432–8.
3. Moody M, Jackowski J. Are patientson oral chemotherapy in your practice setting safe?Clin J Oncol Nurs. 2010, 14: 339-346.
4. Chabrier M, Bezy O, Mouret MA, Bay JO, Jalenques I. Impact of depressive disorders on adherence to oral anti-cancer treatment. Bulletin Du Cancer. 2013; 10: 1017-1022.
5. Burhenn, P.S.; Smudde, J. Using tools and technology to promote education and adherence to oral agents for cancer. Clin. J. Oncol. Nurs. 2015, 19, 53–59.
6. MEDICINE, U.S. National Library Of MEDICINE. Medical Subject Headings: Mobile Applications. 2018. Evaluable in: <https://www.ncbi.nlm.nih.gov/mesh/68063731>. Accessed in: March 16. 2019.
7. Elliott M, Liu Y. The nine rights of medication administration: an overview. Br J Nurs. 2010;19(5):300-5
8. Zerillo JA, Goldenberg BA, Kotecha RR, Tewari AK, Jacobson JO, Krzyzanowska MK 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.
9. Makubi A, Sasi P, Ngaeje M, et al. Rationale and design ofmDOT-HuAstudy: a randomized trial to assess the effect of mobile-directly observed therapy on adherence to hydroxyurea in adults with sickle cell anemia in Tanzania. BMC Med Res Methodol. 2016;16(1):140.
10. Thakkar J, Kurup R, Laba, T, et al. Mobile Telephone Text Messaging for Medication Adherence in Chronic Disease: A Meta-analysis. JAMA Internal Medicine. 2016:176(3):340-349.
11. Barillet M, Prevost V, Joly F, Clarisse B. Oral antineoplasticagents: How do wecareaboutadherence? Br J ClinPharmacol2015;80:1289-302.

For peer review only

12. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA GroupPreferredreportingitems for systematic reviews and meta-analyses: The PRISMA Statement PLoSMed, 6 (2008), p. e1000097. doi: 10.1371/journal.pmed.1000097
13. Shimada CS. Adherence to treatment with oral medications. Rio de Janeiro: Elsevier, 2016.
14. RuddyK,Mayer E, PartridgeA. Patientadherenceandpersistencewith oral anticancertreatment. CA Cancer J Clin2009;59:56–66.
15. Jingjin, Grant ES, Vernon MS Oh, Shuchuen li. Factor saffecting the rapeutic compliance: A review from the patient's perspective. TherClin Risk Manag. 2008; 4(1): 269-286.
16. Higgins, PTJ, Altman, DG, Gotzsche, PC, Juni, P, Moher, D, Oxman, AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. BMJ. 2011; 343, d5928.
17. Jupp JCY, Sultani H, Cooper CA, Peterson KA, Truong TH. Evaluation of mobile phone applications to support medication adherence and symptom management in oncology patients. Pediatric Blood & Cancer. 2018;65(11):e27278.
18. Carmody JK, Denson LA, Hommel KA. Content and Usability Evaluation of Medication Adherence Mobile Applications for Use in Pediatrics. J Pediatr Psychol. 2019 Apr 1;44(3):333-342.

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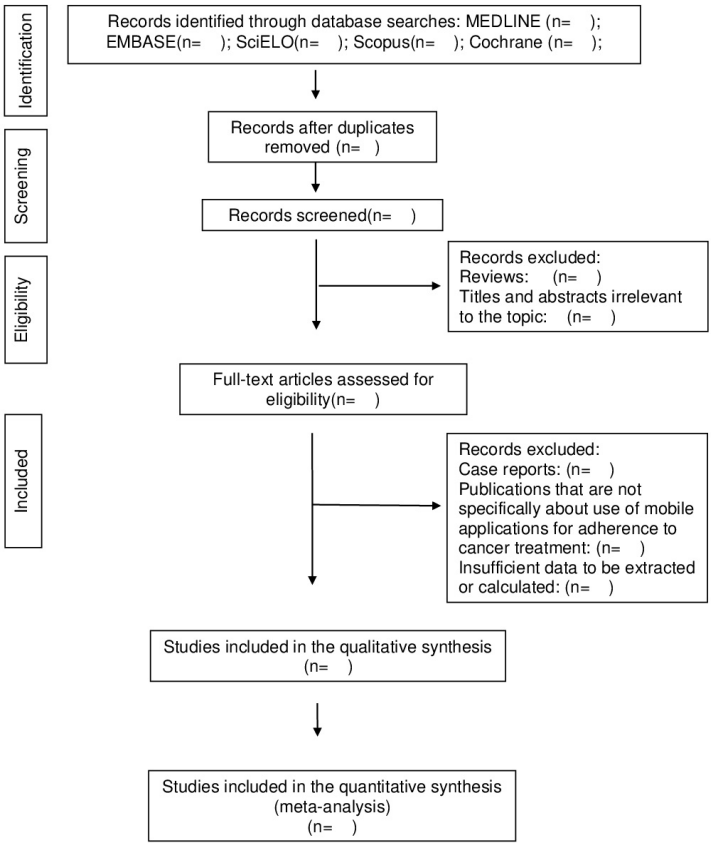

Figure 1 Flow diagram of the search for eligible studies in the use of mobile applications for adherence to cancer treatment: CENTRAL, Cochrane Central Register of Controlled Trials.

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The Impact of Mobile Applications on Adherence to Cancer Treatment: a Systematic Review and Meta-analysis Protocol

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The Impact of Mobile Applications on Adherence to Cancer Treatment: a Systematic Review and Meta-analysis Protocol

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Conflict of Interest statement: None

ABSTRACT

Introduction

The number of patients taking oral chemotherapy is increasing around the world. It is essential to maximize adherence to oral chemotherapy to improve overall survival and life expectancy. This systematic review aims to evaluate the effectiveness of mobile applications in the improvement of adherence to oral chemotherapy and adjuvant hormonal therapy among cancer survivors.

Methods and analysis

The databases MEDLINE, Embase, LILACS, clinicaltrials.gov, Scopus and Cochrane Central Register of Controlled Trials will be used to search for any studies where there was randomization or quasi-experimental designs using mobile applications among cancer survivors to aid adherence to oral chemotherapy and adjuvant hormonal therapy from 2009 to July 2019. Other interventions such as: patient education, reminder tools, calendars, pillboxes and electronic reminders will not be evaluated. The primary outcome will be the improved adherence to medication in cancer treatment. The secondary outcomes will be an improvement in overall survival and life expectancy, improved quality of life and control of symptoms related to cancer. Three independent reviewers will select trials and extract data from the original publications. The risk of bias will be assessed according to the Cochrane Risk of Bias tool. Data synthesis will be performed using the Review Manager software (RevMan V.5.2.3). To assess heterogeneity, we will compute the I^2 statistic. Additionally, a quantitative synthesis will be used if the included studies are sufficiently homogenous.

Ethics and dissemination

This study will be a review of the published data, and thus it is not necessary to obtain ethical approval. Findings of this systematic review will be published in a peer-reviewed journal.

Trial registration number: International Prospective Register of Systematic Reviews 2018: CRD42018102172.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review/meta-analysis aims to combine the results of different studies that have comparable effect sizes that can be computed.
- Three reviewers will independently select the eligibility trials to be included in this review, extract data without different variables and assess the risk of bias.
- However, it may be that we will only get a small sample size and a limited number of studies, which may influence the validity and reliability of the findings.
- Additionally, different types of mobile app may cause considerable heterogeneity that could be deficient in generating convincing conclusions.
- Despite these limitations, the results obtained from this systematic review and meta-analysis will propose which strategy is most useful for the improvement of adherence to oral chemotherapeutic treatment, choosing between the mobile app and other approaches.

INTRODUCTION

Description of the condition

About 25% of new antineoplastic agents in development are estimated to be oral drugs, and the number of available oral chemotherapy medications is expected to more than double over the next few years (1-3). Patients often prefer oral therapy to IV therapy for several reasons. The benefits of oral agents for cancer are: patient preference, convenience of use, easier administration and more convenience for patients because they result in fewer office visits and less time is spent receiving treatment compared to IV chemotherapy (4,5). Additionally, oral therapy can provide a feeling of control over treatment, decrease treatment interference with work and social activities, eliminating the travel time needed to go to an infusion clinic, and eliminate the discomfort of having an IV line inserted for each administration (2). Once an antineoplastic agent is ordered, the administration is the responsibility of the patient (5). Yet patients and clinicians face new challenges in managing adherence to these oral therapies (6).

Although, a substantial proportion of patients struggle to adhere to these medications as prescribed. No reliable estimate of adherence to oral antineoplastic therapies can be obtained from the literature, due to the fact that

the few intervention studies for adherence that there are have notable methodological concerns, thereby limiting the evidence to guide the practice in promoting medication adherence among patients with cancer (6). Thus, the problem of non-adherence to treatment and pharmacological limitations are still poorly studied (3).

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).

Moreover, a variety of educational, symptom management and reminder- based interventions, which involve delivery mechanisms such as face-to-face interactions, phone calls and SMS texting have been developed and tested. However, the evidence on the effectiveness of the interventions is not yet conclusive (9-11).

Description of the intervention

The American Society of Clinical Oncology/Oncology Nursing Society recommend patient education in the oral chemotherapy administration (12).

Patient education includes:

- The storage, handling, preparation, administration, and disposal of oral chemotherapy;
- Concurrent cancer treatment and supportive care medications/measures (when applicable);
- Possible drug/drug and drug/food interactions;
- The plan for missed doses (12).

In this context, oncology nurses can use tools and technology to assist with education, which may promote adherence with the suggestion of reminder tools that can be used. Many have already been developed: patient education; physical devices such as pillboxes and glowing pill bottles; or computer and mobile applications (apps) to work as electronic reminders, such as calendars, text messaging, and alarms (5, 13-14).

In this sense, there are mobile applications that are computer programs or software installed on mobile electronic devices which support a wide range of functions and uses, which include television, telephone, video, music, word processing, and internet service (15). The first medication reminder apps were developed in 2009 (5,6).

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).

Therefore, this protocol aims to verify if the use of mobile applications improves the patient adherence to medication in cancer treatment.

Intervention mechanisms

In the treatment of chronic diseases, drug adherence remains a complicated issue. (8-14,16-18). In these situations, the benefits of using technology as an enabling factor are recognized, even if it is a simple text message (19). This may improve adherence to the prescribed dosage, with an increase in adherence rates ranging from 50% to 67.8% (14).

Apps are suitable for delivering various educational and behavioral interventions while enabling caregivers and health professionals to monitor patients' medication consumption patterns (10).

Why it is important to perform this review

Traditional interventions to improve adherence and that are effective for long-term care are complex and not widely used. There is a widespread need for

convenient and feasible innovations to help patients remain adherent to medications (18).

Presently, the average rate of non-adherence to oral anti-cancer therapy is estimated to be around 21% (4), demonstrating that poor adherence is a barrier to completing the treatment (18,19). Non-adherence is complex and systemic, as well as this, while at home there is no professional oversight to know whether patients are correctly taking the medication as prescribed. Oral regimens may come with complicated dosing schedules or various foods and drug interactions that make adherence difficult. In busy clinics, patients may be given written materials about the new medication, but little time may be available for one-on-one interaction (5). Ensuring patient adherence to a treatment that involves self-administration is a challenge that is faced by health care providers (2,20). Many factors can affect the treatment adherence: lack of understanding regarding proper administration, complex dosing regimens, administration of other potentially interacting medications, the timing of treatment doses concerning food intake, cost of the drug, and unpleasant side effects. Furthermore, common health conditions of the patients such as visual and cognitive impairment, memory deficits or forgetfulness can pose other difficulties (2).

Poor adherence has been linked to successive hospitalizations, increased need for medical interventions, morbidity, and mortality. As well as this, medication non-adherence results in increased health care costs, with North America having estimates of approximately $100 billion being spent annually and $2000 spent per patient per year in excess physician visits (19).

In this context, it is necessary to verify if the use of mobile applications can help the patient to overcome those difficulties and improve the adherence to treatment. Despite the increased use of oral chemotherapy, the number of studies addressing the issue of adherence remains surprisingly low (20).

Objectives

This systematic review and meta-analysis protocol aims to evaluate the effectiveness of mobile applications in the improvement of adherence to oral chemotherapy and adjuvant hormonal therapy among cancer survivors.

Materials and methods

This protocol is registered with the International Prospective Register of Systematic Reviews, registration number CRD42018102172. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (21) statement guidelines were used to construct this systematic review protocol. The number for the International Prospective Register of Systematic Reviews 2018: CRD42018102172.

Types of studies

This systematic review will include studies that fall into these criteria: studies where there was randomization or with quasi-experimental designs; that include adult subjects (above 18 years of age); that evaluate the use of mobile applications for adherence to oral chemotherapy and adjuvant hormonal therapy among cancer survivors; and no language restrictions.

The PICO strategy

- Population/Participants: Patients undergoing oncological treatment with oral chemotherapy or adjuvant hormonal therapy
- Intervention: Use of mobile application
- Comparator/control: Non-use of mobile application
- Outcome: Improvement adherence to medication in cancer treatment.

Types of patients

Participants of the studies are adults (older than 18 years) diagnosed with cancer, ongoing oral chemotherapy or adjuvant hormonal therapy and using mobile applications to improve their adherence to medication.

Types of interventions

Studies that compare the use of the mobile application with a concurrent control group to evaluate adherence.

Types of outcome measures

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).

Search methods for identification of studies

Electronic searches

The Cochrane Central Register of Controlled Trials in The Cochrane Library, clinicaltrials.gov, Medline, LILACS, Scopus and Embase will be used to search for articles dated from 2009 to July 2019. No language restrictions will be used. The MESH terms will be: (antineoplastic agents OR oral anticancer agents OR drug therapy) AND (mobile application OR mobile apps OR app OR smartphone OR health informatics OR mobile health) AND (medication adherence OR patient empowerment OR treatment adherence and compliance).

Other sources

The scope of the computerized literature search may be enlarged based on the reference lists of retrieved articles.

Search strategy

Table 1 presents the search strategy for Medline.

Table 1 Medline search strategy

Search items	
1	antineoplastic agents

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6	mobile apps
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8	health informatics
9	mobile health
10	Or/5-9
11	medication adherence
12	patient participation
13	patient compliance
14	treatment adherence and compliance
15	MedicationTherapy Management
16	Or/11-15
17	4 and 10 and 16

Data collection and analysis

Selection of studies

Three authors, KSM, WAC, and JFQ, will independently screen the search results using titles and abstracts. Duplicates and reviews will be removed from the database. Two reviewers, KSM and MNM will then go through the full text to determine whether they meet the inclusion criteria. Discrepancies will be resolved by a third reviewer, AKG. The selection of the studies is summarized in a PRISMA flow diagram (figure 1).

Insert **Figure 1:** PRISMA flow diagram.

Data extraction and management

Various study characteristics will be extracted from the original research and included in the systematic review and meta-analysis. The data to be included are the first authors' last names, year of publication, location of the study (country), study design, primary objective, population, sample size, follow-up

period, inclusion/exclusion criteria, type of MA used, type of control used, and primary results. Standardized data extraction forms will specifically be created for this review and the results will be subsequently entered into a database. All data entries will be double-checked.

Addressing missing data

We will attempt to obtain any missing data by contacting the first or corresponding authors or coauthors of an article via phone, email or post. If we fail to receive any necessary information, the data will be excluded from our analysis and will be addressed in the discussion section.

Risk of bias assessment

Three review authors, KSM, JFQ and BS, will independently assess the risk of bias in the included studies using the Cochrane risk of bias tool (25). The modified Cochrane Collaboration tool will be used to assess risk of bias. Bias is assessed as a judgment (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other).

Assessment of heterogeneity

The heterogeneity between trial results will be evaluated using a standard X^2 test with a significance level of $p<0.1$. To assess heterogeneity, we plan to compute the I^2 statistic, which is a quantitative measurement of inconsistency across studies. A value of 0% indicates no observed heterogeneity, whereas I^2 values of ≥ 50% indicate a substantial level of heterogeneity; however, the assessment of heterogeneity will only occur if it is appropriate to undertake a meta-analysis.

Analysis

Data will be entered in the Review Manager software (RevMan5.2.3). This software allows the user to enter protocols, to complete reviews, include text, characteristics of the studies, comparison tables and study data, and to perform meta-analyses of the data. For dichotomous outcomes, we will extract or calculate the odds ratio (OR) and 95% confidence interval (CI) for each study. Where there is heterogeneity (I^2 ≥ 50%), a random-effect model will be used to

combine the trials to calculate the OR and 95% CI, using the DerSimonian-Laird algorithm in The Meta for Package, a meta-analysis package for R software.

Other study characteristics and results will be summarized narratively, if the meta-analysis cannot be performed for all or some of the included studies.
Sensitivity analyses will be important to explore the robustness of the findings regarding the study quality and sample size, and this is only possible to consider if a meta-analysis is undertaken. This will be shown in a summary table.

Confidence in cumulative evidence

To describe the strength of evidence for included data, we will use the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach to incorporate summary assessments into broader measurements to ensure the judgments about bias risk, consistency, directness, precision and publication bias (26).

Patient and Public Involvement

The research will be performed using a wide and comprehensive search of literature from databases and the individual patient data will not be included. Ethical approval is not required because this systematic review will use published patient data.

DISCUSSION

The adherence to cancer treatment is a very common and relevant clinical problem, with a significant adverse impact on the health system. In this review, we aim to determine the effect of mobile applications in the improvement of adherence to medication in cancer treatment. In theory, MA can improve adherence to cancer treatment, because they can remind the patient of the time to take the medicine and assist in the management of care. Therefore, MA may support oncology patients with medication and disease management (27, 28). We expect that our review will provide accurate data for effective strategies for adherence to cancer treatment. Furthermore, this review will improve our understanding of adherence to cancer treatment with mobile applications.

Data sharing

Findings of this systematic review will be published in a peer-reviewed journal and updates will be conducted if there is enough new evidence that may cause any change in the review conclusions.

Acknowledgments

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Contributors

KM, BS and AG contributed to the design of this review. KM drafted the protocol manuscript, and AG revised it. KM, RC and AG developed the search strategies and KM, JQ and MM will implement them. KM, MM, JQ, and WC will track potential studies, extract data and assess quality. In case of disagreement between the data extractors, AG will advise on the methodology and will work as the referee. RC will complete the data synthesis. All authors have approved the final version for publication.

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Competing interests

None declared.

Patient consent for publication

Not required.

REFERENCES

1. Weingart SN, Flug J, Brouillard D, Morway L, Partridge A, Bartel S, Shulman LN, Connor M. Oral chemotherapy safety practices at US cancer centers: questionnaire survey. BMJ. 2007 Feb 24;334(7590):407.
2. Wood L. A review on adherence management in patients on oral cancer therapies. Eur J Oncol Nurs. 2012 Sep;16(4):432-8.
3. Moody M, Jackowski J. Are patientson oral chemotherapy in your practice setting safe? Clin J Oncol Nurs. 2010 Jun;14(3):339-46.
4. Chabrier M, Bezy O, Mouret MA, Bay JO, Jalenques I. Impact of depressive disorders on adherence to oral anti-cancer treatment. Bull Cancer. 2013 Oct;100(10):1017-22.
5. Burhenn, P.S.; Smudde, J. Using tools and technology to promote education and adherence to oral agents for cancer. Clin J Oncol Nurs. 2015 Jun;19(3 Suppl):53-9.
6. Greer JA, Amoyal N, Nisotel L, Fishbein JN, MacDonald J, Stagl J, Lennes I, Temel JS, Safren SA, Pirl WF. A Systematic Review of Adherence to Oral Antineoplastic Therapies. Oncologist. 2016 Mar;21(3):354-76.
7. Hershman DL, Kushi LH, Hillyer GC, Coromilas E, Buono D, Lamerato L, Bovbjerg DH, Mandelblatt JS, Tsai WY, Zhong X, Jacobson JS, Wright JD, Neugut AI. Psychosocial factors related to non-persistence with adjuvant endocrine therapy among women with breast cancer: the Breast Cancer Quality of Care Study (BQUAL). Breast Cancer Res Treat. 2016 May;157(1):133-43.
8. Mathes T, Antoine SL, Pieper D, Eikermann M. Adherence enhancing interventions for oral anticancer agents: a systematic review. Cancer Treat Rev. 2014 Feb;40(1):102-8.
9. Ali EE, Chan SSL, Leow JL, Chew L, Yap KY. User acceptance of an app-based adherence intervention: Perspectives from patients taking oral anticancer medications. J Oncol Pharm Pract. 2019 Mar;25(2):390-397.
10. Ali EE, Chan SSL, Poh HY, Susanto YA, Suganya T, Leow JL, Pang CK, Chew L, Yap KY. Design Considerations in the Development of App-Based Oral Anticancer Medication Management Systems: a Qualitative Evaluation of Pharmacists' and Patients' Perspectives. J Med Syst. 2019 Feb 6;43(3):63.

11. Fishbein JN, Nisotel LE, MacDonald JJ, Amoyal Pensak N, Jacobs JM, Flanagan C, Jethwani K, Greer JA. Mobile Application to Promote Adherence to Oral Chemotherapy and Symptom Management: A Protocol for Design and Development. JMIR Res Protoc. 2017 Apr 20;6(4):e62.
12. Neuss MN, Polovich M, McNiff K, Esper P, Gilmore TR, LeFebvre KB, Schulmeister L, Jacobson JO. 2013 updated American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards including standards for the safe administration and management of oral chemotherapy. J Oncol Pract. 2013 Mar;9(2 Suppl):5s-13s.
13. Darlow S, Wen K. Development testing of mobile health interventions for cancer patient self-management: A review. Health Informatics J. 2015 Apr 27:1-18.
14. Jacobs JM, Pensak NA, Sporn NJ, MacDonald JJ, Lennes IT, Safren SA, Pirl WF, Temel JS, Greer JA.Treatment Satisfaction and Adherence to Oral Chemotherapy in Patients With Cancer. J Oncol Pract. 2017 May;13(5):e474-e485.
15. MEDICINE, U.S. National Library Of MEDICINE. Medical Subject Headings: Mobile Applications. 2018. Evaluable in: <https://www.ncbi.nlm.nih.gov/mesh/68063731>. Accessed in: March 16. 2019.
16. Elliott M, Liu Y. The nine rights of medication administration: an overview. Br J Nurs. 2010 Mar 11-24;19(5):300-5.
17. Zerillo JA, Goldenberg BA, Kotecha RR, Tewari AK, Jacobson JO, Krzyzanowska MK Interventions to Improve Oral Chemotherapy Safety and Quality: A Systematic Review.JAMA Oncol. 2018 Jan 1;4(1):105-117.
18. Makubi A, Sasi P, Ngaeje M, et al. Rationale and design ofmDOT-HuAstudy: a randomized trial to assess the effect of mobile-directly observed therapy on adherence to hydroxyurea in adults with sickle cell anemia in Tanzania. BMC Med Res Methodol. 2016 Oct 18;16(1):140.
19. Thakkar J, Kurup R, Laba, T, et al. Mobile Telephone Text Messaging for Medication Adherence in Chronic Disease: A Meta-analysis. JAMA Intern Med. 2016 Mar;176(3):340-9.

20. Barillet M, Prevost V, Joly F, Clarisse B. Oral antineoplastic agents: How do we care about adherence? Br J Clin Pharmacol. 2015 Dec;80(6):1289-302.
21. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement PLoS Med. 2009 Jul 21;6(7):e1000097.
22. Shimada CS. Adherence to treatment with oral medications. Rio de Janeiro: Elsevier, 2016.
23. RuddyK, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. CA Cancer J Clin. 2009 Jan-Feb;59(1):56-66.
24. Jingjin, Grant ES, Vernon MS Oh, Shuchuen li S. Factor saffecting therapeutic compliance: A review from the patient's perspective. Ther Clin Risk Manag. 2008 Feb;4(1):269-86.
25. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Cochrane Bias Methods Group; Cochrane Statistical Methods Group. BMJ. 2011 Oct18;343:d5928.
26. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011 Apr;64(4):401-6.
27. Jupp JCY1,2, Sultani H3, Cooper CA4, Peterson KA5, Truong TH1,6. Evaluation of mobile phone applications to support medication adherence and symptom management in oncology patients. Pediatr Blood Cancer. 2018 Nov;65(11):e27278.
28. Carmody JK, Denson LA, Hommel KA. Content and Usability Evaluation of Medication Adherence Mobile Applications for Use in Pediatrics. J Pediatr Psychol. 2019 Apr 1;44(3):333-342.

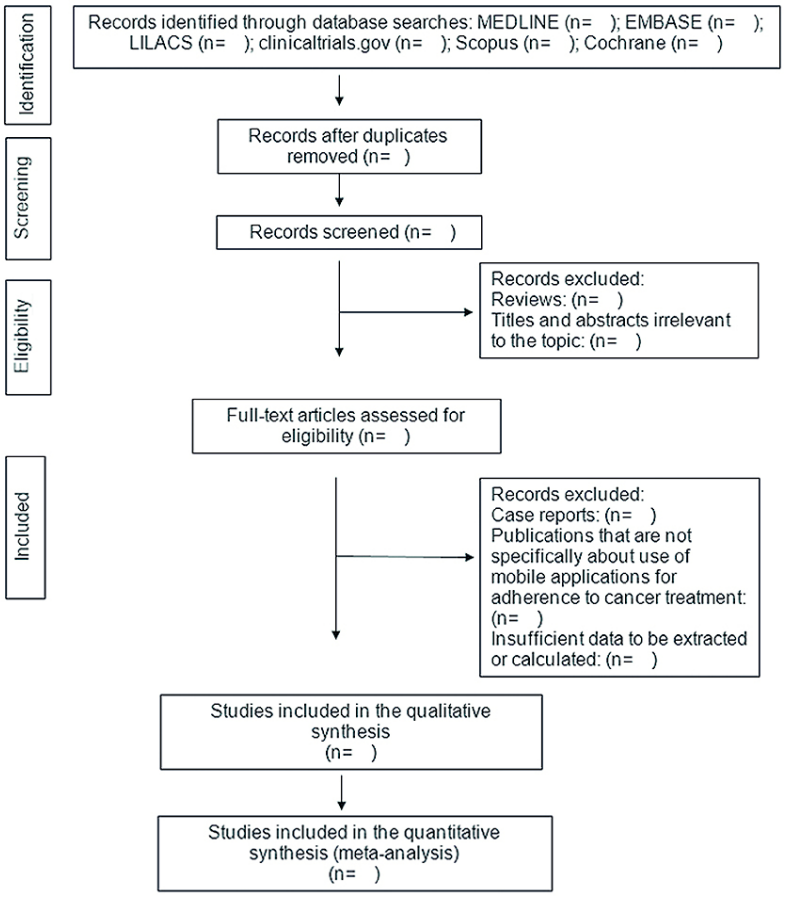

Figure 1 Flow diagram of the search for eligible studies in the use of mobile applications for adherence to cancer treatment: CENTRAL, Cochrane Central Register of Controlled Trials.

Figure 1 Flow diagram of the search for eligible studies in the use of mobile applications for adherence to cancer treatment: CENTRAL, Cochrane Central Register of Controlled Trials.

90x90mm (300 x 300 DPI)

Additional File 1. PRISMAChecklist

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L &Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews*20165:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	√		2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		√	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	√		64
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	√		4-21
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	√		397-404
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		√	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	√		406-409
Sponsor	5b	Provide name for the review funder and/or sponsor		√	N/A
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		√	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	√		200-233
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	√		255-260
METHODS					

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	√		248-260
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	√		284-292
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	√		288-302; Table 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review		√	313-321
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	√		329-334
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	√		313-321
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	√		255-260
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	√		271-281
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	√		329-334
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	√		285-295
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	√		345-360
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	√		345-360
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	√		355-360
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	√		329-334

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	√		362-367

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BMJ Open

The Impact of Mobile Applications on Adherence to Cancer Treatment: a Systematic Review and Meta-analysis Protocol

Journal:	*BMJ Open*
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Complete List of Authors:	Medeiros, Kleyton ; Universidade Federal do Rio Grande do Norte Queiroz, Janice; Universidade Federal do Rio Grande do Norte Centro de Ciencias da Saude Monteiro, Michelly; Universidade Federal do Rio Grande do Norte Costa, Weruska; Universidade Federal do Rio Grande do Norte Centro de Ciencias da Saude Cobucci, Ricardo; Universidade Potiguar Unidade Salgado Filho Stransky, Beatriz; Universidade Federal do Rio Grande do Norte Centro de Tecnologia Gonçalves, Ana ; Universidade Federal do Rio Grande do Norte
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Communication, Nursing
Keywords:	mobile application, medication adherence, oral anticancer agents, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, patient compliance

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The Impact of Mobile Applications on Adherence to Cancer Treatment: a Systematic Review and Meta-analysis Protocol

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Conflict of Interest statement: None

ABSTRACT

Introduction

The number of patients taking oral chemotherapy is increasing around the world. It is essential to maximize adherence to oral chemotherapy to improve overall survival and life expectancy. This systematic review aims to evaluate the effectiveness of mobile applications in the improvement of adherence to oral chemotherapy and adjuvant hormonal therapy among cancer survivors.

Methods and analysis

The databases MEDLINE, Embase, LILACS, clinicaltrials.gov, Scopus and Cochrane Central Register of Controlled Trials will be used to search for any studies where there was randomization or quasi-experimental designs using mobile applications among cancer survivors to aid adherence to oral chemotherapy and adjuvant hormonal therapy from 2009 to July 2019. Other interventions such as: patient education, reminder tools, calendars, pillboxes and electronic reminders will not be evaluated. The primary outcome will be the improved adherence to medication in cancer treatment. The secondary outcomes will be an improvement in overall survival and life expectancy, improved quality of life and control of symptoms related to cancer. Three independent reviewers will select trials and extract data from the original publications. The risk of bias will be assessed according to the Cochrane Risk of Bias tool. Data synthesis will be performed using the Review Manager software (RevMan V.5.2.3). To assess heterogeneity, we will compute the I^2 statistic. Additionally, a quantitative synthesis will be used if the included studies are sufficiently homogenous.

Ethics and dissemination

This study will be a review of the published data, and thus it is not necessary to obtain ethical approval. Findings of this systematic review will be published in a peer-reviewed journal.

Trial registration number: International Prospective Register of Systematic Reviews (PROSPERO) 2018: CRD42018102172.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review/meta-analysis aims to combine the results of different studies that have comparable effect sizes that can be computed.
- Three reviewers will independently select the eligibility trials to be included in this review, extract data without different variables and assess the risk of bias.
- However, it may be that we will only get a small sample size and a limited number of studies, which may influence the validity and reliability of the findings.
- Additionally, different types of mobile app may cause considerable heterogeneity that could be deficient in generating convincing conclusions.
- Despite these limitations, the results obtained from this systematic review and meta-analysis will propose which strategy is most useful for the improvement of adherence to oral chemotherapeutic treatment, choosing between the mobile app and other approaches.

INTRODUCTION

Description of the condition

About 25% of new antineoplastic agents in development are estimated to be oral drugs, and the number of available oral chemotherapy medications is expected to more than double over the next few years (1-3). Patients often prefer oral therapy to IV therapy for several reasons. The benefits of oral agents for cancer are patient preference, convenience of use, easier administration and more convenience for patients because they result in fewer office visits and less time is spent receiving treatment compared to IV chemotherapy (4,5). Additionally, oral therapy can provide a feeling of control over treatment, decrease treatment interference with work and social activities, eliminating the travel time needed to go to an infusion clinic, and eliminate the discomfort of having an IV line inserted for each administration (2). Once an antineoplastic agent is ordered, the administration is the responsibility of the patient (5). Yet patients and clinicians face new challenges in managing adherence to these oral therapies (6).

Although most of the patients attempt to adhere to these medications as prescribed, there is adherence problem yet. No reliable estimate of adherence to oral antineoplastic therapies can be obtained from the literature, due to the

fact that the few intervention studies for adherence that there are have notable methodological concerns, thereby limiting the evidence to guide the practice in promoting medication adherence among patients with cancer (6). Thus, the problem of non-adherence to treatment and pharmacological limitations are still poorly studied (3).

Hershman et al. (7) found that interventions to enhance the psychosocial well-being of patients should be evaluated to increase adherence. Furthermore, the authors explain 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).

Moreover, a variety of educational, symptom management and reminder- based interventions, which involve delivery mechanisms such as face-to-face interactions, phone calls and SMS texting have been developed and tested. However, the evidence on the effectiveness of the interventions is not yet conclusive (9-11).

Description of the intervention

The American Society of Clinical Oncology/Oncology Nursing Society recommend patient education in the oral chemotherapy administration (12).

Patient education includes:

- The storage, handling, preparation, administration, and disposal of oral chemotherapy;
- Concurrent cancer treatment and supportive care medications/measures (when applicable);
- Possible drug/drug and drug/food interactions;
- The plan for missed doses (12).

In this context, oncology nurses can use tools and technology to assist with education, which may promote adherence with the suggestion of reminder tools that can be used. Many have already been developed: patient education; physical devices such as pillboxes and glowing pill bottles; or computer and mobile applications (apps) to work as electronic reminders, such as calendars, text messaging, and alarms (5, 13-14).

In this sense, there are mobile applications (MA) that are computer programs or software installed on mobile electronic devices which support a wide range of functions and uses, which include television, telephone, video, music, word processing, and internet service (15). The first medication reminder apps were developed in 2009 (5,6).

The advantages of 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).

Therefore, this protocol aims to verify if the use of mobile applications improves the patient adherence to medication in cancer treatment.

Intervention mechanisms

In the treatment of chronic diseases, drug adherence remains a complicated issue. (8-14,16-18). In these situations, the benefits of using technology as an enabling factor are recognized, even if it is a simple text message (19). This may improve adherence to the prescribed dosage, with an increase in adherence rates ranging from 50% to 67.8% (14).

Apps are suitable for delivering various educational and behavioral interventions while enabling caregivers and health professionals to monitor patients' medication consumption patterns (10).

Why it is important to perform this review

Traditional interventions to improve adherence and that are effective for long-term care are complex and not widely used. There is a widespread need for convenient and feasible innovations to help patients remain adherent to medications (18).

Presently, the average rate of non-adherence to oral anti-cancer therapy is estimated to be around 21% (4), demonstrating that poor adherence is a barrier to completing the treatment (18,19). Non-adherence is complex and systemic, as well as this, while at home there is no professional oversight to know whether patients are correctly taking the medication as prescribed. Oral regimens may come with complicated dosing schedules or various foods and drug interactions that make adherence difficult. In busy clinics, patients may be given written materials about the new medication, but little time may be available for one-on-one interaction (5). Ensuring patient adherence to a treatment that involves self-administration is a challenge that is faced by health care providers (2,20). Many factors can affect the treatment adherence: lack of understanding regarding proper administration, complex dosing regimens, administration of other potentially interacting medications, the timing of treatment doses concerning food intake, cost of the drug, and unpleasant side effects. Furthermore, common health conditions of the patients such as visual and cognitive impairment, memory deficits or forgetfulness can pose other difficulties (2).

Poor adherence has been linked to successive hospitalizations, increased need for medical interventions, morbidity, and mortality. As well as this, medication non-adherence results in increased health care costs, with North America having estimates of approximately $100 billion being spent annually and $2000 spent per patient per year in excess physician visits (19).

In this context, it is necessary to verify if the use of mobile applications can help the patient to overcome those difficulties and improve the adherence to treatment. Despite the increased use of oral chemotherapy, the number of studies addressing the issue of adherence remains surprisingly low (20).

Objectives

This systematic review and meta-analysis protocol aims to evaluate the effectiveness of mobile applications in the improvement of adherence to oral chemotherapy and adjuvant hormonal therapy among cancer survivors.

Materials and methods

This protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42018102172. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (21) statement guidelines were used to construct this systematic review protocol.

Types of studies

This systematic review will include studies that fall into these criteria: studies where there was randomization or with quasi-experimental designs; that include adult subjects (above 18 years of age); that evaluate the use of mobile applications for adherence to oral chemotherapy and adjuvant hormonal therapy among cancer survivors; and no language restrictions.

The PICO strategy

- Population/Participants: Patients undergoing oncological treatment with oral chemotherapy or adjuvant hormonal therapy
- Intervention: Use of mobile application
- Comparator/control: Non-use of mobile application
- Outcome: Improvement adherence to medication in cancer treatment.

Types of patients

Participants of the studies are adults (older than 18 years) diagnosed with cancer, ongoing oral chemotherapy or adjuvant hormonal therapy and using mobile applications to improve their adherence to medication.

Types of interventions

Studies that compare the use of the mobile application with a concurrent control group to evaluate adherence.

Types of outcome measures

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).

Search methods for identification of studies

Electronic searches

The Cochrane Central Register of Controlled Trials in The Cochrane Library, clinicaltrials.gov, Medline, LILACS, Scopus and Embase will be used to search for articles dated from 2009 to July 2019. No language restrictions will be used. The MESH terms will be: (antineoplastic agents OR oral anticancer agents OR drug therapy) AND (mobile application OR mobile apps OR app OR smartphone OR health informatics OR mobile health) AND (medication adherence OR patient empowerment OR treatment adherence and compliance).

Other sources

The scope of the computerized literature search may be enlarged based on the reference lists of retrieved articles.

Search strategy

Table 1 presents the search strategy for Medline.

Table 1 Medline search strategy

Search items	
1	antineoplastic agents
2	oral anticancer agents
3	drug therapy
4	Or/1-3
5	mobile application

6	mobile apps
7	Smartphone
8	health informatics
9	mobile health
10	Or/5-9
11	medication adherence
12	patient participation
13	patient compliance
14	treatment adherence and compliance
15	MedicationTherapy Management
16	Or/11-15
17	4 and 10 and 16

Data collection and analysis

Selection of studies

Three authors, KSM, WAC, and JFQ, will independently screen the search results using titles and abstracts. Duplicates and reviews will be removed from the database. Two reviewers, KSM and MNM will then go through the full text to determine whether they meet the inclusion criteria. Discrepancies will be resolved by a third reviewer, AKG. The selection of the studies is summarized in a PRISMA flow diagram (figure 1).

Insert **Figure 1:** PRISMA flow diagram.

Data extraction and management

Various study characteristics will be extracted from the original research and included in the systematic review and meta-analysis. The data to be included are the first authors' last names, year of publication, location of the study (country), study design, primary objective, population, sample size, follow-up period, inclusion/exclusion criteria, type of MA used, type of control used, and primary results. Standardized data extraction forms will specifically be created for this review and the results will be subsequently entered into a database. All data entries will be double-checked.

Addressing missing data

We will attempt to obtain any missing data by contacting the first or corresponding authors or coauthors of an article via phone, email or post. If we fail to receive any necessary information, the data will be excluded from our analysis and will be addressed in the discussion section.

Risk of bias assessment

Three review authors, KSM, JFQ and BS, will independently assess the risk of bias in the included studies using the Cochrane risk of bias tool (25). The modified Cochrane Collaboration tool will be used to assess risk of bias. Bias is assessed as a judgment (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other).

Assessment of heterogeneity

The heterogeneity between trial results will be evaluated using a standard X^2 test with a significance level of $p<0.1$. To assess heterogeneity, we plan to compute the I^2 statistic, which is a quantitative measurement of inconsistency across studies. A value of 0% indicates no observed heterogeneity, whereas I^2 values of ≥ 50% indicate a substantial level of heterogeneity; however, the assessment of heterogeneity will only occur if it is appropriate to undertake a meta-analysis.

Analysis

Data will be entered in the Review Manager software (RevMan5.2.3). This software allows the user to enter protocols, to complete reviews, include text, characteristics of the studies, comparison tables and study data, and to perform meta-analyses of the data. For dichotomous outcomes, we will extract or calculate the odds ratio (OR) and 95% confidence interval (CI) for each study. Where there is heterogeneity (I^2 ≥ 50%), a random-effect model will be used to combine the trials to calculate the OR and 95% CI, using the DerSimonian-Laird algorithm in The Meta for Package, a meta-analysis package for R software.

Other study characteristics and results will be summarized narratively, if the meta-analysis cannot be performed for all or some of the included studies.
Sensitivity analyses will be important to explore the robustness of the findings regarding the study quality and sample size, and this is only possible to consider if a meta-analysis is undertaken. This will be shown in a summary table.

Confidence in cumulative evidence

To describe the strength of evidence for included data, we will use the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach to incorporate summary assessments into broader measurements to ensure the judgments about bias risk, consistency, directness, precision and publication bias (26).

Patient and Public Involvement

The research will be performed using a wide and comprehensive search of literature from databases and the individual patient data will not be included. Ethical approval is not required because this systematic review will use published patient data.

DISCUSSION

The adherence to cancer treatment is a very common and relevant clinical problem, with a significant adverse impact on the health system. In this review, we aim to determine the effect of mobile applications in the improvement of adherence to medication in cancer treatment. In theory, MA can improve adherence to cancer treatment, because they can remind the patient of the time to take the medicine and assist in the management of care. Therefore, MA may support oncology patients with medication and disease management (27, 28). We expect that our review will provide accurate data for effective strategies for adherence to cancer treatment. Furthermore, this review will improve our understanding of adherence to cancer treatment with mobile applications.

Ethics and dissemination

Ethical approval is not required because this systematic review will use published patient data. Findings of this systematic review will be published in a peer-reviewed journal and updates will be conducted if there is enough new evidence that may cause any changes in the conclusions of the review.

Data sharing

All data used in the writing of an article review will be cited in the reference list – whether they are data generated by the author(s) or by other researchers. That is, data are publicly available; these will be cited in the reference list.

Findings of this systematic review will be published in a peer-reviewed journal and updates will be conducted if there is enough new evidence that may cause any change in the review conclusions.

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Contributors

KM, BS and AG contributed to the design of this review. KM drafted the protocol manuscript, and AG revised it. KM, RC and AG developed the search strategies and KM, JQ and MM will implement them. KM, MM, JQ, and WC will track potential studies, extract data and assess quality. In case of disagreement between the data extractors, AG will advise on the methodology and will work as the referee. RC will complete the data synthesis. All authors have approved the final version for publication.

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Competing interests

None declared.

Patient consent for publication

Not required.

REFERENCES

1. Weingart SN, Flug J, Brouillard D, Morway L, Partridge A, Bartel S, Shulman LN, Connor M. Oral chemotherapy safety practices at US cancer centers: questionnaire survey. BMJ. 2007 Feb 24;334(7590):407.
2. Wood L. A review on adherence management in patients on oral cancer therapies. Eur J Oncol Nurs. 2012 Sep;16(4):432-8.
3. Moody M, Jackowski J. Are patientson oral chemotherapy in your practice setting safe? Clin J Oncol Nurs. 2010 Jun;14(3):339-46.
4. Chabrier M, Bezy O, Mouret MA, Bay JO, Jalenques I. Impact of depressive disorders on adherence to oral anti-cancer treatment. Bull Cancer. 2013 Oct;100(10):1017-22.
5. Burhenn, P.S.; Smudde, J. Using tools and technology to promote education and adherence to oral agents for cancer. Clin J Oncol Nurs. 2015 Jun;19(3 Suppl):53-9.
6. Greer JA, Amoyal N, Nisotel L, Fishbein JN, MacDonald J, Stagl J, Lennes I, Temel JS, Safren SA, Pirl WF. A Systematic Review of Adherence to Oral Antineoplastic Therapies. Oncologist. 2016 Mar;21(3):354-76.
7. Hershman DL, Kushi LH, Hillyer GC, Coromilas E, Buono D, Lamerato L, Bovbjerg DH, Mandelblatt JS, Tsai WY, Zhong X, Jacobson JS, Wright JD, Neugut AI. Psychosocial factors related to non-persistence with adjuvant endocrine therapy among women with breast cancer: the Breast Cancer Quality of Care Study (BQUAL). Breast Cancer Res Treat. 2016 May;157(1):133-43.
8. Mathes T, Antoine SL, Pieper D, Eikermann M. Adherence enhancing interventions for oral anticancer agents: a systematic review. Cancer Treat Rev. 2014 Feb;40(1):102-8.
9. Ali EE, Chan SSL, Leow JL, Chew L, Yap KY. User acceptance of an app-based adherence intervention: Perspectives from patients taking oral anticancer medications. J Oncol Pharm Pract. 2019 Mar;25(2):390-397.
10. Ali EE, Chan SSL, Poh HY, Susanto YA, Suganya T, Leow JL, Pang CK, Chew L, Yap KY. Design Considerations in the Development of App-Based Oral Anticancer Medication Management Systems: a Qualitative

Evaluation of Pharmacists' and Patients' Perspectives. J Med Syst. 2019 Feb 6;43(3):63.

11. Fishbein JN, Nisotel LE, MacDonald JJ, Amoyal Pensak N, Jacobs JM, Flanagan C, Jethwani K, Greer JA. Mobile Application to Promote Adherence to Oral Chemotherapy and Symptom Management: A Protocol for Design and Development. JMIR Res Protoc. 2017 Apr 20;6(4):e62.
12. Neuss MN, Polovich M, McNiff K, Esper P, Gilmore TR, LeFebvre KB, Schulmeister L, Jacobson JO. 2013 updated American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards including standards for the safe administration and management of oral chemotherapy. J Oncol Pract. 2013 Mar;9(2 Suppl):5s-13s.
13. Darlow S, Wen K. Development testing of mobile health interventions for cancer patient self-management: A review. Health Informatics J. 2015 Apr 27:1-18.
14. Jacobs JM, Pensak NA, Sporn NJ, MacDonald JJ, Lennes IT, Safren SA, Pirl WF, Temel JS, Greer JA.Treatment Satisfaction and Adherence to Oral Chemotherapy in Patients With Cancer. J Oncol Pract. 2017 May;13(5):e474-e485.
15. MEDICINE, U.S. National Library Of MEDICINE. Medical Subject Headings: Mobile Applications. 2018. Evaluable in: <https://www.ncbi.nlm.nih.gov/mesh/68063731>. Accessed in: March 16. 2019.
16. Elliott M, Liu Y. The nine rights of medication administration: an overview. Br J Nurs. 2010 Mar 11-24;19(5):300-5.
17. Zerillo JA, Goldenberg BA, Kotecha RR, Tewari AK, Jacobson JO, Krzyzanowska MK Interventions to Improve Oral Chemotherapy Safety and Quality: A Systematic Review.JAMA Oncol. 2018 Jan 1;4(1):105-117.
18. Makubi A, Sasi P, Ngaeje M, et al. Rationale and design ofmDOT-HuAstudy: a randomized trial to assess the effect of mobile-directly observed therapy on adherence to hydroxyurea in adults with sickle cell anemia in Tanzania. BMC Med Res Methodol. 2016 Oct 18;16(1):140.

19. Thakkar J, Kurup R, Laba, T, et al. Mobile Telephone Text Messaging for Medication Adherence in Chronic Disease: A Meta-analysis. JAMA Intern Med. 2016 Mar;176(3):340-9.
20. Barillet M, Prevost V, Joly F, Clarisse B. Oral antineoplastic agents: How do we care about adherence? Br J Clin Pharmacol. 2015 Dec;80(6):1289-302.
21. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement PLoS Med. 2009 Jul 21;6(7):e1000097.
22. Shimada CS. Adherence to treatment with oral medications. Rio de Janeiro: Elsevier, 2016.
23. RuddyK, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. CA Cancer J Clin. 2009 Jan-Feb;59(1):56-66.
24. Jingjin, Grant ES, Vernon MS Oh, Shuchuen li S. Factor saffecting therapeutic compliance: A review from the patient's perspective. Ther Clin Risk Manag. 2008 Feb;4(1):269-86.
25. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Cochrane Bias Methods Group; Cochrane Statistical Methods Group. BMJ. 2011 Oct18;343:d5928.
26. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011 Apr;64(4):401-6.
27. Jupp JCY1,2, Sultani H3, Cooper CA4, Peterson KA5, Truong TH1,6. Evaluation of mobile phone applications to support medication adherence and symptom management in oncology patients. Pediatr Blood Cancer. 2018 Nov;65(11):e27278.
28. Carmody JK, Denson LA, Hommel KA. Content and Usability Evaluation of Medication Adherence Mobile Applications for Use in Pediatrics. J Pediatr Psychol. 2019 Apr 1;44(3):333-342.

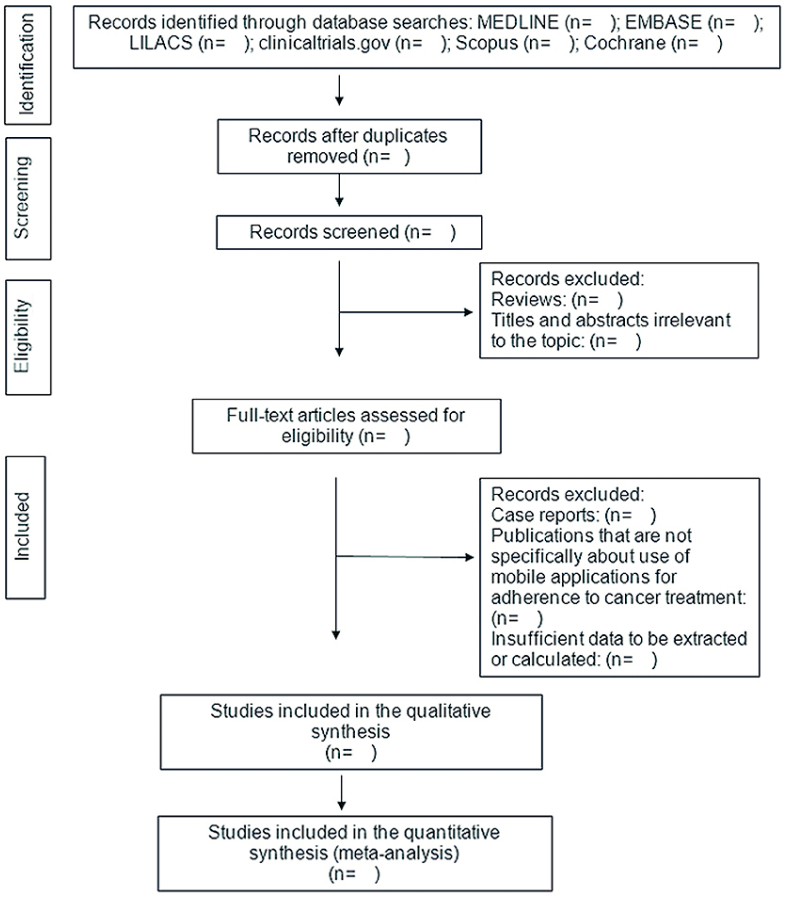

Figure 1 Flow diagram of the search for eligible studies in the use of mobile applications for adherence to cancer treatment: CENTRAL, Cochrane Central Register of Controlled Trials.

Figure 1 Flow diagram of the search for eligible studies in the use of mobile applications for adherence to cancer treatment: CENTRAL, Cochrane Central Register of Controlled Trials.

90x90mm (300 x 300 DPI)

Additional File 1. PRISMAChecklist

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L &Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews*20165:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	√		2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		√	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	√		64
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	√		4-21
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	√		397-404
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		√	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	√		406-409
Sponsor	5b	Provide name for the review funder and/or sponsor		√	N/A
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		√	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	√		200-233
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	√		255-260
METHODS					

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	√		248-260
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	√		284-292
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	√		288-302; Table 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review		√	313-321
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	√		329-334
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	√		313-321
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	√		255-260
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	√		271-281
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	√		329-334
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	√		285-295
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	√		345-360
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	√		345-360
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	√		355-360
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	√		329-334

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	√		362-367

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BMJ Open

The Impact of Mobile Applications on Adherence to Cancer Treatment: a Systematic Review and Meta-analysis Protocol

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Communication, Nursing
Keywords:	mobile application, medication adherence, oral anticancer agents, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, patient compliance

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Manuscripts

The impact of mobile applications on adherence to cancer treatment: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction

The number of patients taking oral chemotherapy is increasing around the world. It is essential to maximize the adherence to oral chemotherapy to improve the overall survival and life expectancy of the patients. In this systematic review and meta-analysis, we aim to evaluate the effectiveness of mobile applications in improving the adherence to oral chemotherapy and adjuvant hormonal therapy in cancer survivors.

Methods and analysis

MEDLINE, Embase, LILACS, clinicaltrials.gov, Scopus, and the Cochrane Central Register of Controlled Trials will be searched for randomized or quasi-experimental studies published between January 2009 and July 2019. This systematic review and meta-analysis will include studies investigating the use of mobile applications by cancer survivors to aid adherence to oral chemotherapy and adjuvant hormonal therapy. Patient education, reminder tools, calendars, pillboxes, and electronic reminders will not be evaluated. The primary outcome will be the improvement in adherence to anti-cancer drugs. The secondary outcomes will be an improvement in the overall survival and life expectancy, improved quality of life, and control of cancer-related symptoms. Three independent reviewers will select the studies and extract data from the original publications. The risk of bias will be assessed using the Cochrane risk-of-bias tool. Data synthesis will be performed using the Review Manager software (RevMan V.5.2.3). To assess heterogeneity, we will compute the I^2 statistics. Additionally, a quantitative synthesis will be performed if the included studies are sufficiently homogenous.

Ethics and dissemination

This study will be a review of the published data, and thus, ethical approval is not required. Findings of this systematic review will be published in a peer-reviewed journal.

Trial registration number: International Prospective Register of Systematic Reviews (PROSPERO) 2018: CRD42018102172.

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Strengths and limitations of this study

- This systematic review and meta-analysis aims to combine the results of different studies that have comparable effect sizes and can be computed.
- Three reviewers will independently select the eligible studies, extract data without different variables, and assess the risk of bias.
- There is a possibility that we get a small sample size and a limited number of studies; this may influence the validity and reliability of the findings.
- Different types of mobile applications may cause considerable heterogeneity that could limit generating convincing conclusions.
- Despite these limitations, the findings of this systematic review and meta-analysis may suggest whether mobile applications or other approaches are more useful in improving the adherence to oral chemotherapeutic treatment.

INTRODUCTION

Description of the condition

About 25% of the new antineoplastic agents under development are estimated to be oral drugs. Notably, the number of oral chemotherapeutic drugs will be more than doubled over the next few years.[1-3] Compared with intravenous (IV) therapy, oral therapy is more convenient, faster and easier to administer, and requires fewer clinic visits and hence, preferred by the patients.[4,5] Additionally, oral therapy can provide a feeling of control over treatment, reduce the interference of treatment with work and social activities, and eliminate the requirement of traveling to an infusion clinic and the discomfort of inserting an IV line.[2] Once an antineoplastic agent is ordered, the administration is the responsibility of the patient.[5] However, patients and clinicians are facing new challenges in managing adherence to these oral therapies.[6]

Most patients attempt to adhere to the treatment according to the prescription, nevertheless, adherence continues to be a problem. It is difficult to obtain a reliable estimate of adherence to oral antineoplastic therapies from the literature. This is because the few intervention studies that have been

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conducted on treatment adherence have notable methodological concerns. Thus, there is limited evidence to promote treatment adherence in patients with cancer.[6] Moreover, studies on non-adherence to treatment and pharmacological limitations are inadequate.[3]

Hershman et al.[7] showed that the interventions to enhance the psychosocial well-being of patients should be evaluated to increase treatment adherence. Furthermore, the authors explained that adherence to therapy has been reported to be associated with belief in the efficacy of the drug and with belief in the benefits of taking prescribed drugs; and a high level of cancer-specific emotional distress was associated with subsequent non-adherence to treatment. Another study suggested that poor physician-patient communication, negative feeling regarding the efficacy of the drugs, and fear of toxicities were associated with failure to initiate the therapy.[6]

In a systematic review, Greer et al.[6] assessed the interventions to improve adherence to oral antineoplastic therapies in patients with various malignancies. These interventions included educational support, monitoring treatment, pharmacy-based programs, counseling programs, and use of pre-filled pillboxes and automated voice response systems. Nevertheless, most of the studies included in this systematic review had a high risk of bias due to non-randomized designs, small sample sizes, subjective assessments of adherence, and missing data. In another systematic review of interventions to promote adherence to oral antineoplastic therapies, the investigators drew similar conclusions, as problems non-adherence to treatment.[8]

A variety of education, symptom management, and reminder-based interventions, which involve face-to-face interactions, phone calls, and texting SMS have been developed and tested. However, the effectiveness of these interventions remains inconclusive.[9-11]

Description of the intervention

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The American Society of Clinical Oncology/Oncology Nursing Society recommends educating patients on the administration of oral chemotherapy (12). This includes the following:

- The storage, handling, preparation, administration, and disposal of oral chemotherapeutic drugs.
- Concurrent anti-cancer treatment and supportive drugs/measures (when applicable).
- Possible drug-drug and drug-food interactions.
- A plan for missed doses.[12]

The oncology nurses can use tools and technology to assist with education, which may promote treatment adherence. In this context, patient education programs, and physical devices such as pillboxes and glowing pill bottles have been developed. Additionally, computer and mobile applications have paved the way for electronic reminders, such as calendars, text messaging, and alarms.[5, 13-14]

Mobile applications are softwares that support a wide range of function of the mobile phone, including television, telephone, video, music, word processing, and internet service.[15] The first drug reminder application was developed in 2009.[5,6] Mobile applications have several advantages compared with other interventions; this include simple and easy use, often in an automated fashion using a computerized program.[6] Thus, mobile applications may be used to encourage healthy lifestyles while monitoring, tracking, collecting, and transmitting data in real-time, facilitating the doctor-patient communication, and increasing the co-operation between the patient and health professionals.[7]

Several techniques may increase treatment adherence, the most effective being behavioral approaches. However, there is no consensus on which behavioral techniques (such as specific goal-setting, self-monitoring, and social comparison) are most effective in promoting treatment adherence.[7]

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With the ever-increasing use of smartphones and development of potentially effective behavioral intervention technologies, scientists may be able to collect data in real-time in a real-world setting. Additionally, researchers are able to optimize the delivery of behavioral interventions and collect data with minimal burden to the patient and provider.[11] Recently, a review suggested that adopting mobile technologies to deliver accessible interventions could improve health behaviors in patients with cancer.[13]

Intervention mechanisms

Adherence remains a complicated issue in the treatment of chronic diseases. [8-14,16-18] In this context, the benefits of using technology, even in the form of a simple text message, have been recognized.[19] This may improve adherence to the prescribed dosage, with an increase in adherence rates ranging from 50% to 67.8%.[14] Mobile applications are suitable for delivering various educational and behavioral interventions while enabling caregivers and health professionals to monitor the patients' drug consumption patterns.[10]

Why it is important to perform this review

The traditional interventions to improve long-term treatment adherence are complex and not widely used. There is a widespread need for innovations that would provide convenient and feasible techniques to help patients remain adherent to the treatment.[18]

Currently, the average rate of non-adherence to oral anti-cancer therapy is estimated to be around 21%.[4] This demonstrates that poor adherence is a barrier to completing the treatment.[18,19] Non-adherence is complex and systemic; moreover, when at home, there is no professional method to know whether patients are correctly taking the drugs as prescribed. Oral regimens may be associated with complicated dosing schedules; additionally, due to food-drug interactions treatment adherence may become difficult. In busy clinics, patients may be given documents about the new drug(s);however, the time available for one-on-one interaction may not be sufficient.[5] Ensuring

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patient adherence to a treatment that involves self-administration is a challenge faced by health care providers.[2,20] Many factors can affect treatment adherence: lack of understanding regarding proper administration, complex dosing regimens, administration of other potentially interacting drugs, the timing of drug doses with respect to food intake, cost of the drug, and unpleasant side effects. Furthermore, common health conditions of the patients such as visual and cognitive impairment, memory deficits, or forgetfulness can pose additional difficulties.[2]

Poor adherence has been linked to successive hospitalization, increased need for medical interventions, morbidity, and mortality. Furthermore, non-adherence results in increased healthcare costs, with North America having estimates of approximately $100 billion being spent annually and $2000 spent per patient per year for additional visits to the physician.[19] It is necessary to verify if the use of mobile applications can help the patients to overcome these difficulties and improve treatment adherence. Despite the increased use of oral chemotherapy, the number of studies addressing the issue of adherence remains surprisingly low.[20]

Objectives

The aim of this systematic review and meta-analysis is to evaluate the effectiveness of mobile applications in improving adherence to oral chemotherapy and adjuvant hormonal therapy in cancer survivors.

METHODS AND ANALYSIS

This protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO); registration number is CRD42018102172. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[21] guidelines were used to design this systematic review protocol.

Inclusion criteria

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This systematic review will include the following studies: those with randomized or quasi-experimental designs; those that include patients aged >18 years; and those that evaluate the use of mobile applications by cancer survivors for adherence to oral chemotherapy and adjuvant hormonal therapy. There will be no language restrictions while selecting the studies.

Patient, intervention, comparison, and outcome strategy

- Patient: those undergoing oral chemotherapy or adjuvant hormonal therapy.
- Intervention: use of mobile applications.
- Comparator/control: no use of mobile applications.
- Outcome: improvement adherence to anti-cancer treatment.

Types of patients

Studies where the patients are aged>18 years, diagnosed with cancer, undergoing oral chemotherapy or adjuvant hormonal therapy, and using mobile applications to improve treatment adherence will be included in this systemic review.

Type of interventions

Studies that compare the use of mobile applications with a concurrent control group to evaluate treatment adherence will be included in this systemic review.

Type of outcome measures

Non-adherence may lead to additional treatment costs due to the increased frequency of hospitalization and medical appointments, recurrence of symptoms, and consequent increase in drug toxicity caused by an overdose (to make up for the missed dose).[4, 22-25]

The primary outcome will be to assess the improvement in treatment adherence.[17] The secondary outcomes will be to assess the improvement in overall survival and life expectancy, improved quality of life, and control of cancer-related symptoms.[9-11]

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Patient and public involvement

This is a protocol for a systematic review and meta-analysis; the research will be conducted based on a wide and comprehensive literature search from relevant databases; the individual patient data will not be included. Thus, patients will not be involved while setting the search terms, in determining outcome measures, implementing study design, and analyzing the results.

Search strategy

The Cochrane Central Register of Controlled Trials, clinicaltrials.gov, Medline, LILACS, Scopus, and Embase will be used to search for articles published between January 2009 and July 2019. We selected the publications starting from January 2009 because the first drug reminder application was developed in 2009.[5,6]

The MESH terms will be: (antineoplastic agents OR oral anticancer agents OR drug therapy) AND (mobile application OR mobile apps OR app OR smartphone OR health informatics OR mobile health) AND (medication adherence OR patient empowerment OR treatment adherence and compliance) [Table 1].

Eligible studies will also be selected from the reference lists of the retrieved articles.

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Table 1 Medline search strategy

Search items	
1	Antineoplastic agents
2	Oral anticancer agents
3	Drug therapy
4	OR/1-3
5	Mobile application
6	Mobile apps
7	Smartphone
8	Health informatics
9	Mobile health
10	OR/5-9
11	Medication adherence
12	Patient participation
13	Patient compliance

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14	Treatment adherence and compliance
15	Medication therapy management
16	OR/11-15
17	4 AND 10 AND 16

Data collection and analysis

Selection of studies

Three authors, KSM, WAC, and JFQ, will independently screen the search results using the titles and abstracts. Duplicate studies and reviews will be excluded. Two reviewers, KSM and MNM, will then go through the full text to determine whether the studies meet the inclusion criteria. Discrepancies will be resolved by a third reviewer, AKG. The selection of the studies is summarized in a PRISMA flow diagram (figure 1).

Insert **Figure 1:** PRISMA flow diagram.

Data extraction and management

Various characteristics of the eligible studies will be extracted, including the first authors' last names, year of publication, location of the study (country), study design, primary objective, population, sample size, follow-up period, inclusion/exclusion criteria, type of mobile application used, type of control, and primary results. Standardized data extraction forms will specifically be created for this review and the results will be subsequently entered into a database. All data entries will be double-checked.

Addressing missing data

We will attempt to obtain any missing data by contacting the first or corresponding authors or coauthors of an article via phone, email, or post. If we

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fail to receive any necessary information, the data will be excluded from our analysis and will be addressed in the discussion section.

Risk of bias assessment

Three authors, KSM, JFQ, and BS, will independently assess the risk of bias in the eligible studies using the Cochrane risk-of-bias tool.[25] The modified Cochrane Collaboration tool will be used to assess the risk of bias. Bias is assessed as a judgment (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other).

Assessment of heterogeneity

The heterogeneity between study results will be evaluated using a standard X^2 test with a significance level of $p<0.1$. To assess heterogeneity, we plan to compute the I^2 statistic, which is a quantitative measurement of inconsistency across studies. A value of 0% indicates no heterogeneity, whereas I^2 values ≥50% indicate a substantial level of heterogeneity; however, heterogeneity will be assessed only if it is appropriate to conduct a meta-analysis.

Analysis

Data will be entered into the Review Manager software (RevMan5.2.3). This software allows the user to enter protocols; complete reviews; include text, characteristics of the studies, comparison tables, and study data; and perform meta-analyses. For dichotomous outcomes, we will extract or calculate the odds ratio (OR) and 95% confidence interval (CI) for each study. In case of heterogeneity (I^2 ≥50%), the random-effects model will be used to combine the studies to calculate the OR and 95% CI, using the DerSimonian-Laird algorithm in the meta for package, which provides functions for conducting meta-analyses in R.

Other study characteristics and results will be summarized narratively if the meta-analysis cannot be performed for all or some of the included studies. Sensitivity analyses will be used to explore the robustness of the findings

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regarding the study quality and sample size. This is only possible if we can conduct a meta-analysis. Sensitivity analyses will be shown in a summary table.

Grading quality of evidence

For grading the strength of evidence from the included data, we will use the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach. The summary of the assessment will be incorporated into broader measurements to ensure the judgment on the risk of bias, consistency, directness, and precision.[26]

DISCUSSION

Non-adherence to cancer treatment is a very common and relevant clinical problem, with a significant adverse impact on the healthcare system. In this systematic review and meta-analysis, we aim to determine the effect of mobile applications on the improvement of treatment adherence in cancer survivors. In theory, mobile applications can improve adherence to anti-cancer treatment, because they can remind the patient to take the medicine on time and assist in care management.[27, 28] We expect that our study will provide accurate data to develop effective strategies for adherence to anti-cancer treatment and help to improve our understanding of the role of mobile applications in this context.

ETHICS AND DISSEMINATION

Ethical approval is not required because this systematic review will use the published data. Findings of this systematic review will be published in a peer-reviewed journal and will be updated if there is enough new evidence to change the conclusions of the systematic review.

Data sharing

Data used in this systematic review will be cited in the reference list, irrespective of whether data is generated by the author(s) or by other researchers. That is, data are publicly available. Findings of this systematic review will be published in a peer-reviewed journal and updates will be

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conducted if there is enough new evidence that may cause any change in the review conclusions.

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Contributors

KSM, BS, and AKG designed this systematic review and meta-analysis. KSM drafted the manuscript, and AKG revised it. KSM, RNC, and AKG developed the search strategies and KSM, JFQ, and MNM will implement it. KSM, MNM, JFQ, and WAC will track potential studies, extract data, and assess the quality; in case of disagreement between the authors, AKG will advise on the methodology and will be the referee. RNC will complete the data synthesis. All authors have approved the final version of this manuscript.

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Competing interests

None declared.

Patient consent for publication

Not required.

REFERENCES

1. Weingart SN, Flug J, Brouillard D, Morway L, Partridge A, Bartel S, Shulman LN, Connor M. Oral chemotherapy safety practices at US cancer centers: questionnaire survey. BMJ. 2007 Feb 24;334(7590):407.
2. Wood L. A review on adherence management in patients on oral cancer therapies. Eur J Oncol Nurs. 2012 Sep;16(4):432-8.

For peer review only

3. Moody M, Jackowski J. Are patientson oral chemotherapy in your practice setting safe? Clin J Oncol Nurs. 2010 Jun;14(3):339-46.
4. Chabrier M, Bezy O, Mouret MA, Bay JO, Jalenques I. Impact of depressive disorders on adherence to oral anti-cancer treatment. Bull Cancer. 2013 Oct;100(10):1017-22.
5. Burhenn, P.S.; Smudde, J. Using tools and technology to promote education and adherence to oral agents for cancer. Clin J Oncol Nurs. 2015 Jun;19(3 Suppl):53-9.
6. Greer JA, Amoyal N, Nisotel L, Fishbein JN, MacDonald J, Stagl J, Lennes I, Temel JS, Safren SA, Pirl WF. A Systematic Review of Adherence to Oral Antineoplastic Therapies. Oncologist. 2016 Mar;21(3):354-76.
7. Hershman DL, Kushi LH, Hillyer GC, Coromilas E, Buono D, Lamerato L, Bovbjerg DH, Mandelblatt JS, Tsai WY, Zhong X, Jacobson JS, Wright JD, Neugut AI. Psychosocial factors related to non-persistence with adjuvant endocrine therapy among women with breast cancer: the Breast Cancer Quality of Care Study (BQUAL). Breast Cancer Res Treat. 2016 May;157(1):133-43.
8. Mathes T, Antoine SL, Pieper D, Eikermann M. Adherence enhancing interventions for oral anticancer agents: a systematic review. Cancer Treat Rev. 2014 Feb;40(1):102-8.
9. Ali EE, Chan SSL, Leow JL, Chew L, Yap KY. User acceptance of an app-based adherence intervention: Perspectives from patients taking oral anticancer medications. J Oncol Pharm Pract. 2019 Mar;25(2):390-397.
10. Ali EE, Chan SSL, Poh HY, Susanto YA, Suganya T, Leow JL, Pang CK, Chew L, Yap KY. Design Considerations in the Development of App-Based Oral Anticancer Medication Management Systems: a Qualitative Evaluation of Pharmacists' and Patients' Perspectives. J Med Syst. 2019 Feb 6;43(3):63.
11. Fishbein JN, Nisotel LE, MacDonald JJ, Amoyal Pensak N, Jacobs JM, Flanagan C, Jethwani K, Greer JA. Mobile Application to Promote Adherence to Oral Chemotherapy and Symptom Management: A Protocol for Design and Development. JMIR Res Protoc. 2017 Apr 20;6(4):e62.
12. Neuss MN, Polovich M, McNiff K, Esper P, Gilmore TR, LeFebvre KB, Schulmeister L, Jacobson JO. 2013 updated American Society of Clinical

For peer review only

Oncology/Oncology Nursing Society chemotherapy administration safety standards including standards for the safe administration and management of oral chemotherapy. J Oncol Pract. 2013 Mar;9(2 Suppl):5s-13s.

13. Darlow S, Wen K. Development testing of mobile health interventions for cancer patient self-management: A review. Health Informatics J. 2015 Apr 27:1-18.
14. Jacobs JM, Pensak NA, Sporn NJ, MacDonald JJ, Lennes IT, Safren SA, Pirl WF, Temel JS, Greer JA.Treatment Satisfaction and Adherence to Oral Chemotherapy in Patients With Cancer. J Oncol Pract. 2017 May;13(5):e474-e485.
15. MEDICINE, U.S. National Library Of MEDICINE. Medical Subject Headings: Mobile Applications. 2018. Evaluable in: <https://www.ncbi.nlm.nih.gov/mesh/68063731>. Accessed in: March 16. 2019.
16. Elliott M, Liu Y. The nine rights of medication administration: an overview. Br J Nurs. 2010 Mar 11-24;19(5):300-5.
17. Zerillo JA, Goldenberg BA, Kotecha RR, Tewari AK, Jacobson JO, Krzyzanowska MK Interventions to Improve Oral Chemotherapy Safety and Quality: A Systematic Review.JAMA Oncol. 2018 Jan 1;4(1):105-117.
18. Makubi A, Sasi P, Ngaeje M, et al. Rationale and design ofmDOT-HuAstudy: a randomized trial to assess the effect of mobile-directly observed therapy on adherence to hydroxyurea in adults with sickle cell anemia in Tanzania. BMC Med Res Methodol. 2016 Oct 18;16(1):140.
19. Thakkar J, Kurup R, Laba, T, et al. Mobile Telephone Text Messaging for Medication Adherence in Chronic Disease: A Meta-analysis. JAMA Intern Med. 2016 Mar;176(3):340-9.
20. Barillet M, Prevost V, Joly F, Clarisse B. Oral antineoplastic agents: How do we care about adherence? Br J Clin Pharmacol. 2015 Dec;80(6):1289-302.
21. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement PLoS Med. 2009 Jul 21;6(7):e1000097.

For peer review only

22. Shimada CS. Adherence to treatment with oral medications. Rio de Janeiro: Elsevier, 2016.
23. RuddyK, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. CA Cancer J Clin. 2009 Jan-Feb;59(1):56-66.
24. Jingjin, Grant ES, Vernon MS Oh, Shuchuen li S. Factor saffecting therapeutic compliance: A review from the patient's perspective. Ther Clin Risk Manag. 2008 Feb;4(1):269-86.
25. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Cochrane Bias Methods Group; Cochrane Statistical Methods Group. BMJ. 2011 Oct18;343:d5928.
26. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011 Apr;64(4):401-6.
27. Jupp JCY, Sultani H, Cooper CA, Peterson KA, Truong TH. Evaluation of mobile phone applications to support medication adherence and symptom management in oncology patients. Pediatr Blood Cancer. 2018 Nov;65(11):e27278.
28. Carmody JK, Denson LA, Hommel KA. Content and Usability Evaluation of Medication Adherence Mobile Applications for Use in Pediatrics. J Pediatr Psychol. 2019 Apr 1;44(3):333-342.

Figure 1: PRISMA flow diagram.

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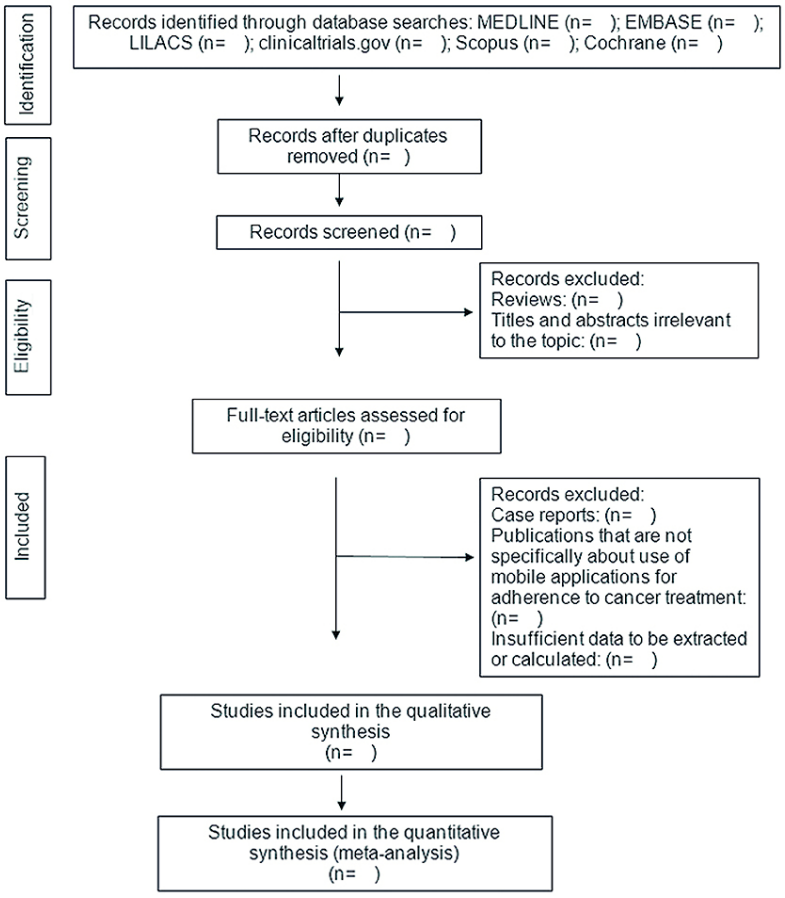

Figure 1 Flow diagram of the search for eligible studies in the use of mobile applications for adherence to cancer treatment: CENTRAL, Cochrane Central Register of Controlled Trials.

Figure 1 Flow diagram of the search for eligible studies in the use of mobile applications for adherence to cancer treatment: CENTRAL, Cochrane Central Register of Controlled Trials.

90x90mm (300 x 300 DPI)

Additional File 1. PRISMAChecklist

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L &Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews*20165:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	√		2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		√	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	√		64
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	√		4-21
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	√		397-404
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		√	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	√		406-409
Sponsor	5b	Provide name for the review funder and/or sponsor		√	N/A
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		√	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	√		200-233
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	√		255-260
METHODS					

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	√		248-260
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	√		284-292
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	√		288-302; Table 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review		√	313-321
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	√		329-334
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	√		313-321
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	√		255-260
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	√		271-281
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	√		329-334
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	√		285-295
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	√		345-360
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	√		345-360
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	√		355-360
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	√		329-334

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	√		362-367

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