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

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SCHOLARONE™
Manuscripts

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3 **1 The Impact of Mobile Applications on Adherence to Cancer Treatment: a**
4 **2 Systematic Review Protocol**
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45 21 Conflict of Interest statement: None
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28 **ABSTRACT**

29 **Introduction**

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

38 **Methods and analysis**

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

53 **Ethics and dissemination**

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

57 **Trial registration number**

58 International Prospective Register of Systematic Reviews 2018:
59 CRD42018102172.

62 **Strengths and limitations of this study**

63 - The results obtained from this systematic review will propose which strategy is
64 most useful for the improvement of adherence to oral chemotherapeutic
65 treatment, choosing between mobile app and others methods.

66 - Two reviewers will independently select the eligibility trials to be included in
67 this review, extract data without different variables and assess the risk of bias

68 - Our review and meta-analysis aims to combine the results of different studies
69 that have comparable effect sizes that can be computed. However, it may be
70 that we will only get a small sample size and a limited number of studies, which
71 may influence the validity and reliability of the findings.

72 - Our review would be limited by variation of strategies for adherence to oral
73 chemotherapy and quality of the randomized trials used in the systematic
74 review.

76 **Introduction**

77 **Description of the condition**

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

93 **Description of the intervention**

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

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3 96 Many have already been developed: patient education; physical devices such
4 97 as pillboxes and glowing pill bottles; or computer and mobile applications (apps)
5 98 to work as electronic reminders, such as calendars, text messaging, and
6 99 alarms (5). This article aims to verify if the use of mobile applications improves
7 100 the patient in adherence to medication in cancer treatment.
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102 **How the intervention might work**

103 Mobile applications are computer programs or software installed on mobile
104 electronic devices which support a wide range of functions and uses which
105 include television, telephone, video, music, word processing, and Internet
106 service (6). Based on the researchers' analysis of available apps, medication
107 reminder apps were first developed in 2009 (5). For the purpose of this study,
108 the mobile application will replicate (or show, inform) the medical and nursing
109 orientations for use of oral chemotherapy drugs at home, i.e., how to take, the
110 principle reactions, and principle interactions. Additionally, they will remind the
111 patient to take the medication at the right time and right dose as prescribed (7).
112

113 **Why it is important to perform this review**

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

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3 130 doses in relation to food intake, cost of the drug, and unpleasant side effects.
4
5 131 Furthermore, common health conditions of the patients such as visual and
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7 132 cognitive impairment, memory deficits or forgetfulness can pose another
8
9 133 difficulties (2). In this context, it is necessary to verify if the use of mobile
10
11 134 applications can help the patient to overcome those difficulties and improve the
12
13 135 adherence to treatment. Despite the increased use of oral chemotherapy, the
14
15 136 number of studies addressing the issue of adherence remains surprisingly low
16
17 137 (11).

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139 **Objectives**

140 The objective of the study is to systematically review and, if possible, perform a
141
142 quantitative meta-analysis to determine the effect of mobile applications in the
143
144 improvement of adherence to medication in cancer treatment.

143

144 **Materials and methods**

145 This protocol is registered with the International Prospective Register of
146
147 Systematic Reviews, registration number CRD42018102172. The Preferred
148
149 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (12)
150
151 statement guidelines were used to construct this systematic review protocol.
152
153 International Prospective Register of Systematic Reviews 2018:
154
155 CRD42018102172.

151

152 **Types of studies**

153 This review will include studies that fall in these criteria: (a) Clinical Trial,
154
155 Controlled Clinical Trial or Randomized Controlled Trial, (b) studies including
156
157 adult subjects (18 years of age); (c) studies published up to January 2018; (d)
158
159 studies including adherence to cancer treatment with oral medications and use
160
161 of mobile applications; (e) clinical trials evaluating the use of mobile applications
162
163 for adherence to oral treatment in cancer patients and (f) no language
164
165 restrictions.

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161 **Types of patients**

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3 162 Participants of the studies are adults (older than 18 years) diagnosed with
4 cancer, using ongoing oral chemotherapy medications and using mobile
5 163 applications to improve their adherence to medication.
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10 166 **Types of interventions**

11 167 Parallel Randomized Controlled Trials (RCTs) that compare the use of the
12 mobile application with a concurrent control group, which does not use the
13 168 mobile application. Other interventions will not be evaluated, for example:
14 patient education, Reminder Tools, Calendars, pillboxes, Electronic Reminders,
15 169 etc. (9,10).
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22 173 **Types of outcome measures**

23 174 The primary outcome will be the improved adherence to medication in cancer
24 treatment. The secondary outcome will be improvement in self-care, better life
25 175 quality and control of signs and symptoms. Another outcome is the success of
26 the therapy instituted by the physician and health team and economic benefits
27 176 (reduction of exacerbation of the disease, crisis or relapse); in the assumption
28 of social and professional roles (13). Consequences of non-adherence are not
29 177 only an increase in consumption resources from the health system, such as the
30 number of medical consultations and emergency consultations, more frequent
31 178 hospitalizations with longer duration, but also an increase in treatment toxicity,
32 bias in the evaluation of drug efficacy and an increase in mortality (4, 14-15).
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43 186 **Search methods for identification of studies**

44 187 **Electronic searches**

45 188 The databases MEDLINE, Embase, SciELO, Scopus and Cochrane Database
46 of Systematic Reviews will be used to search for articles. No language
47 189 restrictions will be used, no restrictions on publication period will be applied.
48 The descriptor terms will be: (antineoplastic agents OR oral anticancer agents
49 190 OR drug therapy) AND (mobile application OR mobile apps OR app OR
50 smartphone OR health informatics OR mobile health) AND (medication
51 191 adherence OR patient empowerment OR treatment adherence and
52 compliance).
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3 196 **Other sources**

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5 197 The scope of the computerized literature search will be enlarged on the basis of
6
7 198 the reference lists of retrieved articles.

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9 199 **Patient and Public Involvement**

10 200 The research will be performed by a wide and comprehensive search of
11
12 201 literature from data bases and the individual patient data are not included. Thus,
13
14 202 the authors no involved patients in setting there search question, as well as, the
15
16 203 outcome measures, the design and implementation of the study, and the
17
18 204 dissemination of its results.

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20 206 **Search strategy**

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22 207 Table 1 presents the search strategy for Medline.

23
24 **Table 1** Medline search strategy

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26 Search items

27	1	antineoplastic agents
28	2	oral anticancer agents
29	3	drug therapy
30	4	Or/1-3
31	5	mobile application
32	6	mobile apps
33	7	smartphone
34	8	health informatics
35	9	mobile health
36	10	Or/5-9
37	11	medication adherence
38	12	patient participation
39	13	patient compliance
40	14	treatment adherence and compliance
41	15	MedicationTherapy Management
42	16	Or/11-15
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59 209 **Data collection and analysis**

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210 **Selection of studies and Search and selection of literature**

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

219
220 Study identification and selection is illustrated in the flow diagram in [Fig. 1](#). After
221 searching the databases, potentially relevant papers will be identified and the
222 others excluded after reviewing the title or after reviewing the abstract. Reviews
223 will be made by KSM, WAC, and JFQ; disagreements will be solved by a fourth
224 reviewer (AKSG). Thus, papers that meet the criteria will be reviewed in full.
225 After the full review, papers that are considered to not have adequate
226 methodological quality according to the GRADE guidelines will be excluded.
227 Finally, repeated studies that are found (being present in two databases at the
228 same time) will be excluded. Finally, papers will be approved for data extraction
229 (Fig. 1).

230
231 Insert **Figure 1**: Flow diagram of the search for eligible studies in the use of
232 mobile applications for adherence to cancer treatment: CENTRAL, Cochrane
233 Central Register of Controlled Trials.

235 **Data extraction and management**

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

1
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3 244 inclusion criteria to choose available articles. Disagreements will be solved by
4
5 245 means of mutual consensus.
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8 247 **Risk of bias assessment**

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10 248 Three review authors will independently assess the risk of bias in the included
11
12 249 studies using the Cochrane risk of bias tool. The modified Cochrane
13
14 250 Collaboration tool will be used to assess risk of bias for randomized controlled
15
16 251 trials. Bias is assessed as a judgment (high, low, or unclear) for individual
17
18 252 elements from five domains (selection, performance, attrition, reporting, and
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20 253 other) (16).
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22 254 **Assessment of heterogeneity**

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24 255 The bias of publication will be mitigated with a comprehensive, sensitive,
25
26 256 unrestricted search for language and with an extensive search in the gray
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28 257 literature.
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31 258 The heterogeneity of the studies will be evaluated in the funnel plot.
32
33 259 Additionally, a quantitative synthesis will be used if the included studies are
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35 260 sufficiently homogenous.

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37 261 As well as this, the heterogeneity between trial results will be evaluated using a
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39 262 standard X^2 test with a significance level of $p < 0.1$. To assess heterogeneity, we
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41 263 plan to compute the I^2 statistic, which is a quantitative measurement of
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43 264 inconsistency across studies. A value of 0% indicates no observed
44
45 265 heterogeneity, whereas I^2 values of $\geq 50\%$ indicate a substantial level of
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47 266 heterogeneity.
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49 267 **Analysis**

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51 268 Data will be entered in the Review Manager software (RevMan5.2). This
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53 269 software allows the user to enter protocols, to complete reviews, include text,
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55 270 characteristics of the studies, comparison tables and study data, and to perform
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57 271 meta-analyses of the data that the Odds Ratios will obtain.
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59 272 **DISCUSSION**

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3 277 The adherence to cancer treatment is a very common and relevant clinical
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5 278 problem, with a significant adverse impact on the health system. In this review,
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7 279 we aim to determine the effect of mobile applications in the improvement of
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9 280 adherence to medication in cancer treatment. In theory, mobile applications can
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11 281 improve adherence to cancer treatment, because it reminds the patient of the
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13 282 time to take the medicine and assists in the management of care. Therefore,
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15 283 mobile phone applications (apps), may support oncology patients with
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17 284 medication and disease management (17). We expect that our review will
18
19 285 provide accurate data for effective strategies for adherence to cancer treatment.
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21 286 Furthermore, this review will improve our understanding of adherence to cancer
22
23 287 treatment with mobile applications.

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289 **Ethics and dissemination**

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

294

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33 363

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369

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

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380 **Competing interests** None declared.

For peer review only

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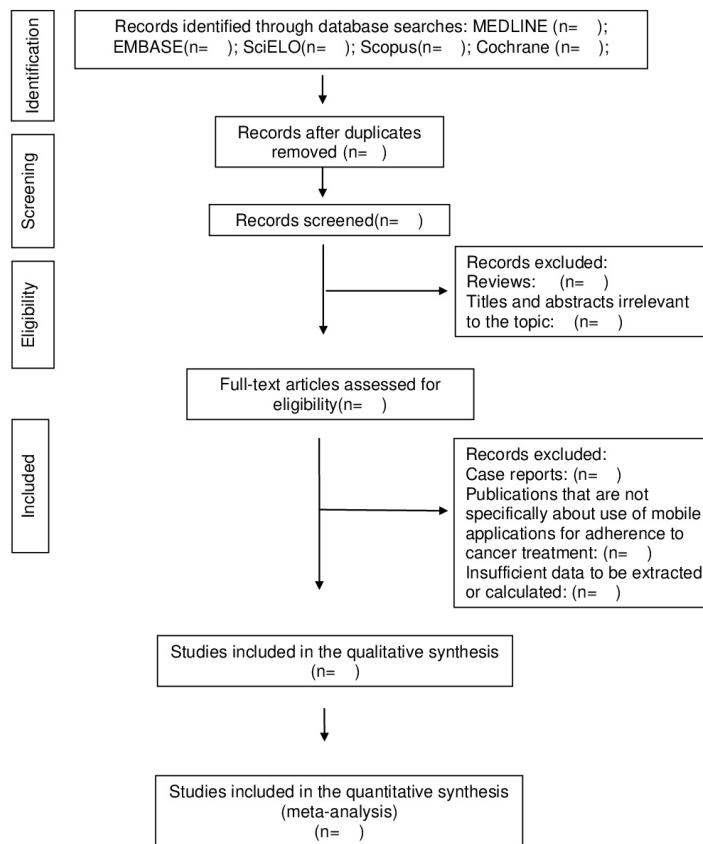


Figure 1 Flow diagram of the search for eligible studies in the use of mobile applications for adherence to cancer treatment: CENTRAL, Cochrane Central Register of Controlled Trials.

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PRISMA 2009 Checklist

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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.	



PRISMA 2009 Checklist

Page 1 of 2

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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Page 2 of 2

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BMJ Open

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

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3 **1 The Impact of Mobile Applications on Adherence to Cancer Treatment: a**
4 **2 Systematic Review Protocol**
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46 21 Conflict of Interest statement: None
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28 **ABSTRACT**

29 **Introduction**

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

35 **Methods and analysis**

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

52 **Ethics and dissemination**

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

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

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62 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

63 - This review/meta-analysis aims to combine the results of different studies that
64 have comparable effect sizes that can be computed.

65 - Three reviewers will independently select the eligibility trials to be included in
66 this review, extract data without different variables and assess the risk of bias.

67 - However, it may be that we will only get a small sample size and a limited
68 number of studies, which may influence the validity and reliability of the findings.

69 - Additionally, different types of mobile app may cause considerable
70 heterogeneity that might be deficient in generating convincing conclusions.

71 - Despite these limitations, the results obtained from this systematic review will
72 propose which strategy is most useful for the improvement of adherence to oral
73 chemotherapeutic treatment, choosing between the mobile app and other
74 approaches.

76 **INTRODUCTION**

77 **Description of the condition**

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

93 **Description of the intervention**

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

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3 96 Many have already been developed: patient education; physical devices such
4 97 as pillboxes and glowing pill bottles; or computer and mobile applications (apps)
5 98 to work as electronic reminders, such as calendars, text messaging, and
6 99 alarms (5). This article aims to verify if the use of mobile applications improves
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10 the patient in adherence to medication in cancer treatment.
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102 **Intervention mechanisms**

103 Mobile applications are computer programs or software installed on mobile
104 electronic devices which support a wide range of functions and uses which
105 include television, telephone, video, music, word processing, and Internet
106 service (6). Based on the researchers' analysis of available apps, medication
107 reminder apps were first developed in 2009 (5). For the purpose of this study,
108 the mobile application will replicate (or show, inform) the medical and nursing
109 orientations for use of oral chemotherapy drugs at home, i.e., how to take, the
110 principle reactions, and principle interactions. Additionally, they will remind the
111 patient to take the medication at the right time and right dose as prescribed (7).
112

112

113 In the treatment of chronic diseases, adherence to treatment remain a
114 complicated issue. (8-10). In these situations, It is recognized the benefit of
115 interventions, even if it is a simple intervention (text message). (10). These
116 interferences increase medication adherence, with a doubling of the odds of
117 patients' achieving adherence to their medication regimens. The latter increase
118 adherence rates from 50% to 67.8%.
119

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120 The advantages of mobile applications over other interventions are simplicity
121 and ease of administration, often in an automated fashion using a computerized
122 program.
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124 Mobile applications may be useful for promoting healthy behaviors and
125 lifestyles, monitor, track, collect and transmit data in real time, facilitating the
126 doctor-patient communication, increasing the level of sharing and cooperation
127 between the patient and health professionals.
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3 129 Several techniques may increase adherence to treatment. The most effective
4 130 interventions include behavioral approaches; however, there is no consensus
5 131 on which behavioral techniques (e.g., specific goal-setting, self-monitoring, and
6 132 social comparison) are central to effective medication adherence interventions.
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11 134 **Why it is important to perform this review**

12 135 Traditional interventions to improve adherence are complex and not widely
13 136 useful. All interventions effective for long-term care were involved and not
14 137 widely useful. There is a widespread need for convenient and feasible
15 138 innovations to help patients remain adherent to medications (10).
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22 140 Presently, the average rate of non-adherence to oral anti-cancer therapy is
23 141 estimated to be around 21% (4); that is, poor adherence is a barrier to
24 142 completing the treatment (9,10). Non-adherence is complex and systemic, as
25 143 well as this, at home there is no professional oversight to know whether patients
26 144 are correctly taking the medication as prescribed. Oral regimens may come with
27 145 complicated dosing schedules or various foods and drug interactions that make
28 146 adherence difficult. In busy clinics, patients may be given written materials
29 147 about the new medication, but little time may be available for one-on-one
30 148 interaction (5). Ensuring patient adherence to a treatment that involves self-
31 149 administration is a challenge that is faced by health care providers (2,11). Many
32 150 factors can affect the treatment adherence: lack of understanding regarding
33 151 proper administration, complex dosing regimens, administration of other
34 152 potentially interacting medications, the timing of treatment doses concerning
35 153 food intake, cost of the drug, and unpleasant side effects. Furthermore,
36 154 common health conditions of the patients such as visual and cognitive
37 155 impairment, memory deficits or forgetfulness can pose other difficulties (2).
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51 157 Poor adherence has been linked to successive hospitalizations, increased need
52 158 for medical interventions, morbidity, and mortality. Besides, medication non-
53 159 adherence results increased health care cost, with estimates from North
54 160 America of approximately \$100 billion being spent annually and \$2000 spent
55 161 per patient per year in excess physician visits (10).
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3 163 In this context, it is necessary to verify if the use of mobile applications can help
4 the patient to overcome those difficulties and improve the adherence to
5 164 treatment. Despite the increased use of oral chemotherapy, the number of
6 165 studies addressing the issue of adherence remains surprisingly low (11).
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11 168 **Objectives**

12
13 169 This review/metanalysis aims to evaluate the effectiveness of mobile
14 applications in the improvement of adherence to oral chemotherapy and
15 170 adjuvant hormonal therapy among cancer survivors.
16
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19 173 **Materials and methods**

20
21 174 This protocol is registered with the International Prospective Register of
22 Systematic Reviews, registration number CRD42018102172. The Preferred
23 175 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (12)
24 176 statement guidelines were used to construct this systematic review protocol.
25
26 177 International Prospective Register of Systematic Reviews 2018:
27 178 CRD42018102172.
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32 182 **Types of studies**

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34 183 This review will include studies that fall in these criteria: (a) Clinical Trial,
35 Controlled Clinical Trial or Randomized Controlled Trial, (b) studies including
36 184 adult subjects (18 years of age); (c) studies published up to July2019; (d)
37 185 studies including adherence to cancer treatment with oral medications and use
38 186 of mobile applications; (e) clinical trials evaluating the use of mobile applications
39 187 for adherence to oral chemotherapy and adjuvant hormonal therapy among
40 188 cancer survivors (f) no language restrictions.
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44 191 **The PICO strategy**

- 45
46 192 • Population/Participants: Patients on oncological treatment with oral
47 193 chemotherapy and adjuvant hormonal therapy among cancer survivors
48
49 194 • Intervention: Use of mobile application
50
51 195 • Comparator/control: Do not use mobile application
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53 196 • Outcome: Improvement adherence to medication in cancer treatment.
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197 **Types of patients**

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

202 **Types of interventions**

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

209 **Types of outcome measures**

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

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

223 Another outcome will be the success of the therapy instituted by the physician
224 and health team and economic benefits (reduction of exacerbation of the
225 disease, crisis or relapse); in the assumption of social and professional roles
226 (13).

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

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

233

234 **Search methods for identification of studies**

235 **Electronic searches**

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

244

245 **Other sources**

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

248

249 **Patient and Public Involvement**

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

255

256 **Search strategy**

257 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

258

259 **Data collection and analysis**

260 **Selection of studies and Search and selection of literature**

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

269

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

1
2
3 278 same time) will be excluded. Finally, papers will be approved for data extraction
4
5 279 (Fig. 1).
6
7 280

8 281 Insert **Figure 1**: Flow diagram of the search for eligible studies in the use of
9
10 282 mobile applications for adherence to cancer treatment: CENTRAL, Cochrane
11
12 283 Central Register of Controlled Trials.
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14 284

15 285 **Data extraction and management**

16 286 Various study characteristics will be extracted from the original research and
17
18 287 included in the systematic review. The data to be included are the first authors'
19
20 288 last names, year of publication, location of the study (country), study design,
21
22 289 primary objective, population, sample size, follow-up period, inclusion/exclusion
23
24 290 criteria, type of App used, type of control used, and primary results.
25
26 291 Standardized data extraction forms will specifically be created for this review
27
28 292 and the results will be subsequently entered into a database. All data entry will
29
30 293 be double-checked. Three blind reviewers (KSM, WAC, and JFQ) use the
31
32 294 inclusion criteria to choose available articles. Disagreements will be solved by
33
34 295 means of mutual consensus.
35
36 296

37 297 **Risk of bias assessment**

38 298 Three review authors will independently assess the risk of bias in the included
39
40 299 studies using the Cochrane risk of bias tool. The modified Cochrane
41
42 300 Collaboration tool will be used to assess risk of bias for randomized controlled
43
44 301 trials. Bias is assessed as a judgment (high, low, or unclear) for individual
45
46 302 elements from five domains (selection, performance, attrition, reporting, and
47
48 303 other) (16).
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50 304

51 305 **Assessment of heterogeneity**

52 306 The bias of publication will be mitigated with a comprehensive, sensitive,
53
54 307 unrestricted search for language and with an extensive search in the gray
55
56 308 literature.
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59 310 The high heterogeneity predicted among the selected articles will occur due to
60 311 the great diversity of protocols for the treatment of cancer and the variety of

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3 312 available mobile applications. The factors that will be compared are better
4
5 313 Adherence and persistence with therapy, safety/toxicity, clinical disease-related
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7 314 outcomes, health care utilization, and patient engagement with some promising
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9 315 signs of improvement.

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11 317 The heterogeneity of the studies will be evaluated in the funnel plot.
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13 318 Additionally, a quantitative synthesis will be used if the included studies are
14
15 319 sufficiently homogenous.

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18 321 As well as this, the heterogeneity between trial results will be evaluated using a
19
20 322 standard X^2 test with a significance level of $p < 0.1$. To assess heterogeneity, we
21
22 323 plan to compute the I^2 statistic, which is a quantitative measurement of
23
24 324 inconsistency across studies. A value of 0% indicates no observed
25
26 325 heterogeneity, whereas I^2 values of $\geq 50\%$ indicate a substantial level of
27
28 326 heterogeneity.

29 327

30 328 **Analysis**

31
32 329 Data will be entered in the Review Manager software (RevMan5.2). This
33
34 330 software allows the user to enter protocols, to complete reviews, include text,
35
36 331 characteristics of the studies, comparison tables and study data, and to perform
37
38 332 meta-analyses of the data that the Odds Ratios will obtain.

39 333

40 334 **DISCUSSION**

41
42 335 The adherence to cancer treatment is a very common and relevant clinical
43
44 336 problem, with a significant adverse impact on the health system. In this review,
45
46 337 we aim to determine the effect of mobile applications in the improvement of
47
48 338 adherence to medication in cancer treatment. In theory, mobile applications can
49
50 339 improve adherence to cancer treatment, because it reminds the patient of the
51
52 340 time to take the medicine and assists in the management of care. Therefore,
53
54 341 mobile phone applications (apps), may support oncology patients with
55
56 342 medication and disease management (17,18). We expect that our review will
57
58 343 provide accurate data for effective strategies for adherence to cancer treatment.
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60 344 Furthermore, this review will improve our understanding of adherence to cancer
345 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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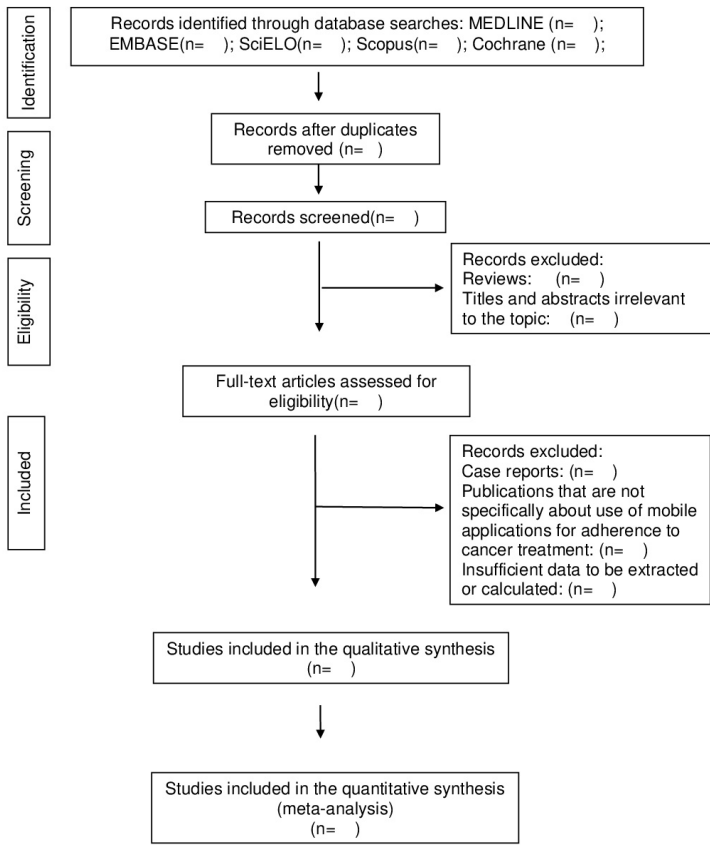


Figure 1 Flow diagram of the search for eligible studies in the use of mobile applications for adherence to cancer treatment: CENTRAL, Cochrane Central Register of Controlled Trials.

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BMJ Open

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

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3 **The Impact of Mobile Applications on Adherence to Cancer Treatment: a**
4 **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 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

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3 the few intervention studies for adherence that there are have notable
4 methodological concerns, thereby limiting the evidence to guide the practice in
5 promoting medication adherence among patients with cancer (6). Thus, the
6 problem of non-adherence to treatment and pharmacological limitations are still
7 poorly studied (3).
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13 Hershman et al. found that interventions to enhance the psychosocial well-being
14 of patients should be evaluated to increase adherence. Furthermore, he
15 explains in his study that adherence to therapy has been reported to be
16 associated with belief in the efficacy of the medication and with belief in the
17 benefits of taking prescribed medications more generally; and high levels of
18 cancer-specific emotional distress were associated with subsequent non-
19 persistence in treatment (7).
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27 Another important finding is that the perception of poor physician–patient
28 communication, negative beliefs regarding efficacy of the medication and fear of
29 toxicities are associated with failure to initiate the therapy (6).
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34 In a systematic review, Greer et al. (6) assessed interventions to improve
35 adherence to oral antineoplastic therapies for patients with various
36 malignancies. Interventions varied in format, and included educational support,
37 treatment monitoring, pharmacy-based programs, counseling programs,
38 prefilled pill boxes, and automated voice response systems. Nevertheless, most
39 of these suffered high risk of bias due to nonrandomized designs, small sample
40 sizes, subjective assessments of adherence, and missing data concerns. In
41 another systematic review of interventions to promote adherence to oral
42 antineoplastic therapies that has been published to date, the investigators drew
43 similar conclusions (8).
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53 Moreover, a variety of educational, symptom management and reminder- based
54 interventions, which involve delivery mechanisms such as face-to-face
55 interactions, phone calls and SMS texting have been developed and tested.
56 However, the evidence on the effectiveness of the interventions is not yet
57 conclusive (9-11).
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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).

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3 Several techniques may increase adherence to treatment. However, most
4 effective interventions include behavioral approaches and there is no
5 consensus on which behavioral techniques (e.g., specific goal setting, self-
6 monitoring, and social comparison) are central to effective medication
7 adherence interventions (7).
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13 With the ever-growing presence of smartphones and the potential for efficacious
14 behavioral intervention technology, scientists may implement momentary
15 interventions and momentary assessments in order to collect data in real-time in
16 real and convenient real-world situations. Along with this, researchers are thus
17 able to optimize the delivery of behavioral interventions and collect ongoing
18 data with minimal burden to the patient and provider (11).
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24 A recent review indicates that adopting mobile technologies to deliver
25 accessible interventions can improve health behaviors in patients with cancer
26 (13).
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31 Therefore, this protocol aims to verify if the use of mobile applications improves
32 the patient adherence to medication in cancer treatment.
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36 **Intervention mechanisms**

37 In the treatment of chronic diseases, drug adherence remains a complicated
38 issue. (8-14,16-18). In these situations, the benefits of using technology as an
39 enabling factor are recognized, even if it is a simple text message (19). This
40 may improve adherence to the prescribed dosage, with an increase in
41 adherence rates ranging from 50% to 67.8% (14).
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48 Apps are suitable for delivering various educational and behavioral interventions
49 while enabling caregivers and health professionals to monitor patients'
50 medication consumption patterns (10).
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55 **Why it is important to perform this review**

56 Traditional interventions to improve adherence and that are effective for long-
57 term care are complex and not widely used. There is a widespread need for
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3 convenient and feasible innovations to help patients remain adherent to
4 medications (18).
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8 Presently, the average rate of non-adherence to oral anti-cancer therapy is
9 estimated to be around 21% (4), demonstrating that poor adherence is a barrier
10 to completing the treatment (18,19). Non-adherence is complex and systemic,
11 as well as this, while at home there is no professional oversight to know
12 whether patients are correctly taking the medication as prescribed. Oral
13 regimens may come with complicated dosing schedules or various foods and
14 drug interactions that make adherence difficult. In busy clinics, patients may be
15 given written materials about the new medication, but little time may be
16 available for one-on-one interaction (5). Ensuring patient adherence to a
17 treatment that involves self-administration is a challenge that is faced by health
18 care providers (2,20). Many factors can affect the treatment adherence: lack of
19 understanding regarding proper administration, complex dosing regimens,
20 administration of other potentially interacting medications, the timing of
21 treatment doses concerning food intake, cost of the drug, and unpleasant side
22 effects. Furthermore, common health conditions of the patients such as visual
23 and cognitive impairment, memory deficits or forgetfulness can pose other
24 difficulties (2).
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39 Poor adherence has been linked to successive hospitalizations, increased need
40 for medical interventions, morbidity, and mortality. As well as this, medication
41 non-adherence results in increased health care costs, with North America
42 having estimates of approximately \$100 billion being spent annually and \$2000
43 spent per patient per year in excess physician visits (19).
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49 In this context, it is necessary to verify if the use of mobile applications can help
50 the patient to overcome those difficulties and improve the adherence to
51 treatment. Despite the increased use of oral chemotherapy, the number of
52 studies addressing the issue of adherence remains surprisingly low (20).
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58 **Objectives**

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

11 This protocol is registered with the International Prospective Register of
12 Systematic Reviews, registration number CRD42018102172. The Preferred
13 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (21)
14 statement guidelines were used to construct this systematic review protocol.
15 The number for the International Prospective Register of Systematic Reviews
16 2018: CRD42018102172.
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24 **Types of studies**

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

- 37 • Population/Participants: Patients undergoing oncological treatment with oral
38 chemotherapy or adjuvant hormonal therapy
- 39 • Intervention: Use of mobile application
- 40 • Comparator/control: Non-use of mobile application
- 41 • Outcome: Improvement adherence to medication in cancer treatment.
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48 **Types of patients**

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

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

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3 period, inclusion/exclusion criteria, type of MA used, type of control used, and
4 primary results. Standardized data extraction forms will specifically be created
5 for this review and the results will be subsequently entered into a database. All
6 data entries will be double-checked.
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10 11 **Addressing missing data**

12 We will attempt to obtain any missing data by contacting the first or
13 corresponding authors or coauthors of an article via phone, email or post. If we
14 fail to receive any necessary information, the data will be excluded from our
15 analysis and will be addressed in the discussion section.
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20 21 **Risk of bias assessment**

22 Three review authors, KSM, JFQ and BS, will independently assess the risk of
23 bias in the included studies using the Cochrane risk of bias tool (25). The
24 modified Cochrane Collaboration tool will be used to assess risk of bias. Bias is
25 assessed as a judgment (high, low, or unclear) for individual elements from five
26 domains (selection, performance, attrition, reporting, and other).
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33 34 **Assessment of heterogeneity**

35 The heterogeneity between trial results will be evaluated using a standard X^2
36 test with a significance level of $p < 0.1$. To assess heterogeneity, we plan to
37 compute the I^2 statistic, which is a quantitative measurement of inconsistency
38 across studies. A value of 0% indicates no observed heterogeneity, whereas I^2
39 values of $\geq 50\%$ indicate a substantial level of heterogeneity; however, the
40 assessment of heterogeneity will only occur if it is appropriate to undertake a
41 meta-analysis.
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49 50 **Analysis**

51 Data will be entered in the Review Manager software (RevMan5.2.3). This
52 software allows the user to enter protocols, to complete reviews, include text,
53 characteristics of the studies, comparison tables and study data, and to perform
54 meta-analyses of the data. For dichotomous outcomes, we will extract or
55 calculate the odds ratio (OR) and 95% confidence interval (CI) for each study.
56 Where there is heterogeneity ($I^2 \geq 50\%$), a random-effect model will be used to
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3 combine the trials to calculate the OR and 95% CI, using the DerSimonian-Laird
4 algorithm in The Meta for Package, a meta-analysis package for R software.
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8 Other study characteristics and results will be summarized narratively, if the
9 meta-analysis cannot be performed for all or some of the included studies.
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11 Sensitivity analyses will be important to explore the robustness of the findings
12 regarding the study quality and sample size, and this is only possible to
13 consider if a meta-analysis is undertaken. This will be shown in a summary
14 table.
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20 **Confidence in cumulative evidence**

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

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

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

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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

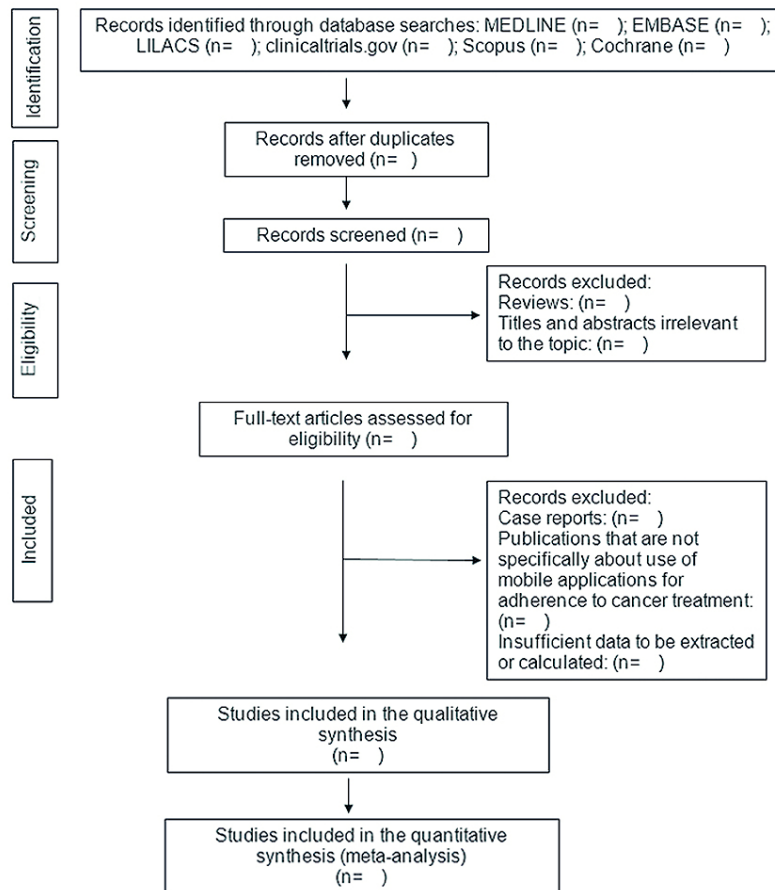
Not required.

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36 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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40 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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Additional File 1. PRISMA Checklist

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* 2016;5:15

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					

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

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

For peer review only

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027246.R3
Article Type:	Protocol
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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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3 **The Impact of Mobile Applications on Adherence to Cancer Treatment: a**
4 **Systematic Review and Meta-analysis Protocol**
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38 Conflict of Interest statement: None
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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

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3 fact that the few intervention studies for adherence that there are have notable
4 methodological concerns, thereby limiting the evidence to guide the practice in
5 promoting medication adherence among patients with cancer (6). Thus, the
6 problem of non-adherence to treatment and pharmacological limitations are still
7 poorly studied (3).
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13 Hershman et al. (7) found that interventions to enhance the psychosocial well-
14 being of patients should be evaluated to increase adherence. Furthermore, the
15 authors explain that adherence to therapy has been reported to be associated
16 with belief in the efficacy of the medication and with belief in the benefits of
17 taking prescribed medications more generally; and high levels of cancer-specific
18 emotional distress were associated with subsequent non-persistence in
19 treatment (7).
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27 Another important finding is that the perception of poor physician–patient
28 communication, negative beliefs regarding efficacy of the medication and fear of
29 toxicities are associated with failure to initiate the therapy (6).
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34 In a systematic review, Greer et al. (6) assessed interventions to improve
35 adherence to oral antineoplastic therapies for patients with various
36 malignancies. Interventions varied in format, and included educational support,
37 treatment monitoring, pharmacy-based programs, counseling programs,
38 prefilled pill boxes, and automated voice response systems. Nevertheless, most
39 of these suffered high risk of bias due to nonrandomized designs, small sample
40 sizes, subjective assessments of adherence, and missing data concerns. In
41 another systematic review of interventions to promote adherence to oral
42 antineoplastic therapies that has been published to date, the investigators drew
43 similar conclusions (8).
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53 Moreover, a variety of educational, symptom management and reminder- based
54 interventions, which involve delivery mechanisms such as face-to-face
55 interactions, phone calls and SMS texting have been developed and tested.
56 However, the evidence on the effectiveness of the interventions is not yet
57 conclusive (9-11).
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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

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3 consensus on which behavioral techniques (e.g., specific goal setting, self-
4 monitoring, and social comparison) are central to effective medication
5 adherence interventions (7).
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10 With the ever-growing presence of smartphones and the potential for efficacious
11 behavioral intervention technology, scientists may implement momentary
12 interventions and momentary assessments in order to collect data in real-time in
13 real and convenient real-world situations. Along with this, researchers are thus
14 able to optimize the delivery of behavioral interventions and collect ongoing
15 data with minimal burden to the patient and provider (11).
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20 A recent review indicates that adopting mobile technologies to deliver
21 accessible interventions can improve health behaviors in patients with cancer
22 (13).
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27 Therefore, this protocol aims to verify if the use of mobile applications improves
28 the patient adherence to medication in cancer treatment.
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32 **Intervention mechanisms**

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34 In the treatment of chronic diseases, drug adherence remains a complicated
35 issue. (8-14,16-18). In these situations, the benefits of using technology as an
36 enabling factor are recognized, even if it is a simple text message (19). This
37 may improve adherence to the prescribed dosage, with an increase in
38 adherence rates ranging from 50% to 67.8% (14).
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44 Apps are suitable for delivering various educational and behavioral interventions
45 while enabling caregivers and health professionals to monitor patients'
46 medication consumption patterns (10).
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51 **Why it is important to perform this review**

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53 Traditional interventions to improve adherence and that are effective for long-
54 term care are complex and not widely used. There is a widespread need for
55 convenient and feasible innovations to help patients remain adherent to
56 medications (18).
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3 Presently, the average rate of non-adherence to oral anti-cancer therapy is
4 estimated to be around 21% (4), demonstrating that poor adherence is a barrier
5 to completing the treatment (18,19). Non-adherence is complex and systemic,
6 as well as this, while at home there is no professional oversight to know
7 whether patients are correctly taking the medication as prescribed. Oral
8 regimens may come with complicated dosing schedules or various foods and
9 drug interactions that make adherence difficult. In busy clinics, patients may be
10 given written materials about the new medication, but little time may be
11 available for one-on-one interaction (5). Ensuring patient adherence to a
12 treatment that involves self-administration is a challenge that is faced by health
13 care providers (2,20). Many factors can affect the treatment adherence: lack of
14 understanding regarding proper administration, complex dosing regimens,
15 administration of other potentially interacting medications, the timing of
16 treatment doses concerning food intake, cost of the drug, and unpleasant side
17 effects. Furthermore, common health conditions of the patients such as visual
18 and cognitive impairment, memory deficits or forgetfulness can pose other
19 difficulties (2).

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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 $\geq 50\%$ 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 ($I^2 \geq 50\%$), 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.

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3 Other study characteristics and results will be summarized narratively, if the
4 meta-analysis cannot be performed for all or some of the included studies.

5 Sensitivity analyses will be important to explore the robustness of the findings
6 regarding the study quality and sample size, and this is only possible to
7 consider if a meta-analysis is undertaken. This will be shown in a summary
8 table.
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13 14 15 **Confidence in cumulative evidence**

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

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

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

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3 Ethical approval is not required because this systematic review will use
4 published patient data. Findings of this systematic review will be published in a
5 peer-reviewed journal and updates will be conducted if there is enough new
6 evidence that may cause any changes in the conclusions of the review.
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10 11 **Data sharing**

12 All data used in the writing of an article review will be cited in the reference list –
13 whether they are data generated by the author(s) or by other researchers. That
14 is, data are publicly available; these will be cited in the reference list.
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20 Findings of this systematic review will be published in a peer-reviewed journal
21 and updates will be conducted if there is enough new evidence that may cause
22 any change in the review conclusions.
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27 **Acknowledgments**

28 The authors acknowledge the assistance provided by the Graduate Program in
29 Health Sciences of the Federal University of Rio Grande do Norte (UFRN) in the
30 undertaking of literary research.
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36 **Contributors**

37 KM, BS and AG contributed to the design of this review. KM drafted the protocol
38 manuscript, and AG revised it. KM, RC and AG developed the search strategies
39 and KM, JQ and MM will implement them. KM, MM, JQ, and WC will track
40 potential studies, extract data and assess quality. In case of disagreement
41 between the data extractors, AG will advise on the methodology and will work
42 as the referee. RC will complete the data synthesis. All authors have approved
43 the final version for publication.
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53 funding agency in the public, commercial or not-for-profit sectors.
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56 **Competing interests**

57 None declared.
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60 **Patient consent for publication**

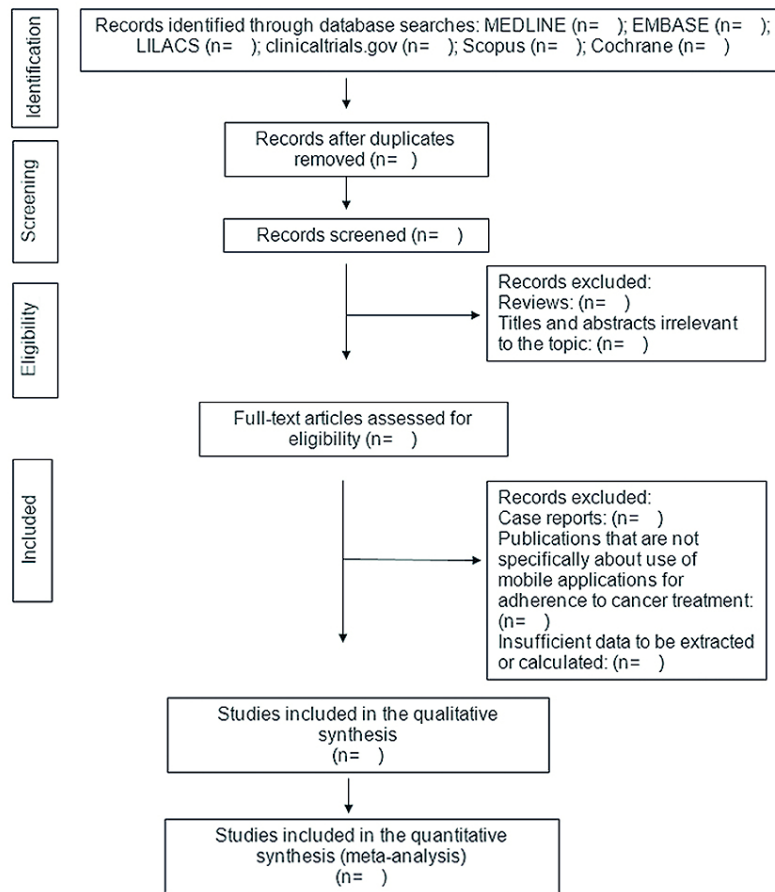
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Figure 1 Flow diagram of the search for eligible studies in the use of mobile applications for adherence to cancer treatment: CENTRAL, Cochrane Central Register of Controlled Trials.

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. PRISMA Checklist

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* 2016;5:15

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					

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

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

For peer review only

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027246.R4
Article Type:	Protocol
Date Submitted by the Author:	14-Sep-2019
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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Manuscripts

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3 **The impact of mobile applications on adherence to cancer treatment: a**
4 **systematic review and meta-analysis protocol**
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8 Kleyton Santos de Medeiros,¹ Janice França Queiroz,¹ Michelly Nóbrega
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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.

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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3 conducted on treatment adherence have notable methodological concerns.
4 Thus, there is limited evidence to promote treatment adherence in patients with
5 cancer.[6] Moreover, studies on non-adherence to treatment and
6 pharmacological limitations are inadequate.[3]
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12 Hershman et al.[7] showed that the interventions to enhance the psychosocial
13 well-being of patients should be evaluated to increase treatment adherence.
14 Furthermore, the authors explained that adherence to therapy has been
15 reported to be associated with belief in the efficacy of the drug and with belief in
16 the benefits of taking prescribed drugs; and a high level of cancer-specific
17 emotional distress was associated with subsequent non-adherence to
18 treatment. Another study suggested that poor physician-patient communication,
19 negative feeling regarding the efficacy of the drugs, and fear of toxicities were
20 associated with failure to initiate the therapy.[6]
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31 In a systematic review, Greer et al.[6] assessed the interventions to improve
32 adherence to oral antineoplastic therapies in patients with various malignancies.
33 These interventions included educational support, monitoring treatment,
34 pharmacy-based programs, counseling programs, and use of pre-filled pillboxes
35 and automated voice response systems. Nevertheless, most of the studies
36 included in this systematic review had a high risk of bias due to non-randomized
37 designs, small sample sizes, subjective assessments of adherence, and
38 missing data. In another systematic review of interventions to promote
39 adherence to oral antineoplastic therapies, the investigators drew similar
40 conclusions, as problems non-adherence to treatment.[8]
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51 A variety of education, symptom management, and reminder-based
52 interventions, which involve face-to-face interactions, phone calls, and texting
53 SMS have been developed and tested. However, the effectiveness of these
54 interventions remains inconclusive.[9-11]
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60 **Description of the intervention**

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3 The American Society of Clinical Oncology/Oncology Nursing Society
4 recommends educating patients on the administration of oral chemotherapy
5 (12). This includes the following:
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- 8 • The storage, handling, preparation, administration, and disposal of oral
9 chemotherapeutic drugs.
- 10 • Concurrent anti-cancer treatment and supportive drugs/measures (when
11 applicable).
- 12 • Possible drug-drug and drug-food interactions.
- 13 • A plan for missed doses.[12]

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21 The oncology nurses can use tools and technology to assist with education,
22 which may promote treatment adherence. In this context, patient education
23 programs, and physical devices such as pillboxes and glowing pill bottles have
24 been developed. Additionally, computer and mobile applications have paved the
25 way for electronic reminders, such as calendars, text messaging, and alarms.[5,
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34 Mobile applications are softwares that support a wide range of function of the
35 mobile phone, including television, telephone, video, music, word processing,
36 and internet service.[15] The first drug reminder application was developed in
37 2009.[5,6] Mobile applications have several advantages compared with other
38 interventions; this include simple and easy use, often in an automated fashion
39 using a computerized program.[6] Thus, mobile applications may be used to
40 encourage healthy lifestyles while monitoring, tracking, collecting, and
41 transmitting data in real-time, facilitating the doctor-patient communication, and
42 increasing the co-operation between the patient and health professionals.[7]
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51 Several techniques may increase treatment adherence, the most effective being
52 behavioral approaches. However, there is no consensus on which behavioral
53 techniques (such as specific goal-setting, self-monitoring, and social
54 comparison) are most effective in promoting treatment adherence.[7]
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3 With the ever-increasing use of smartphones and development of potentially
4 effective behavioral intervention technologies, scientists may be able to collect
5 data in real-time in a real-world setting. Additionally, researchers are able to
6 optimize the delivery of behavioral interventions and collect data with minimal
7 burden to the patient and provider.[11] Recently, a review suggested that
8 adopting mobile technologies to deliver accessible interventions could improve
9 health behaviors in patients with cancer.[13]

17 **Intervention mechanisms**

19 Adherence remains a complicated issue in the treatment of chronic diseases.
20 [8-14,16-18] In this context, the benefits of using technology, even in the form of
21 a simple text message, have been recognized.[19] This may improve
22 adherence to the prescribed dosage, with an increase in adherence rates
23 ranging from 50% to 67.8%.[14] Mobile applications are suitable for delivering
24 various educational and behavioral interventions while enabling caregivers and
25 health professionals to monitor the patients' drug consumption patterns.[10]

33 **Why it is important to perform this review**

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

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

1
2
3 patient adherence to a treatment that involves self-administration is a challenge
4 faced by health care providers.[2,20] Many factors can affect treatment
5 adherence: lack of understanding regarding proper administration, complex
6 dosing regimens, administration of other potentially interacting drugs, the timing
7 of drug doses with respect to food intake, cost of the drug, and unpleasant side
8 effects. Furthermore, common health conditions of the patients such as visual
9 and cognitive impairment, memory deficits, or forgetfulness can pose additional
10 difficulties.[2]

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

36 **Objectives**

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

45 **METHODS AND ANALYSIS**

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

57 **Inclusion criteria**

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3 This systematic review will include the following studies: those with randomized
4 or quasi-experimental designs; those that include patients aged >18 years; and
5 those that evaluate the use of mobile applications by cancer survivors for
6 adherence to oral chemotherapy and adjuvant hormonal therapy. There will be
7 no language restrictions while selecting the studies.
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13 **Patient, intervention, comparison, and outcome strategy**

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

18 **Types of patients**

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

27 Studies that compare the use of mobile applications with a concurrent control
28 group to evaluate treatment adherence will be included in this systemic review.
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35 **Type of outcome measures**

36 Non-adherence may lead to additional treatment costs due to the increased
37 frequency of hospitalization and medical appointments, recurrence of
38 symptoms, and consequent increase in drug toxicity caused by an overdose (to
39 make up for the missed dose).[4, 22-25]
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45 The primary outcome will be to assess the improvement in treatment
46 adherence.[17] The secondary outcomes will be to assess the improvement in
47 overall survival and life expectancy, improved quality of life, and control of
48 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.

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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4 **14** Treatment adherence and compliance
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7 **15** Medication therapy management
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11 **16** OR/11-15
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14 **17** 4 AND 10 AND 16
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17 18 19 20 **Data collection and analysis**

21 22 **Selection of studies**

23
24 Three authors, KSM, WAC, and JFQ, will independently screen the search
25 results using the titles and abstracts. Duplicate studies and reviews will be
26 excluded. Two reviewers, KSM and MNM, will then go through the full text to
27 determine whether the studies meet the inclusion criteria. Discrepancies will be
28 resolved by a third reviewer, AKG. The selection of the studies is summarized in
29 a PRISMA flow diagram (figure 1).
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36 Insert **Figure 1**: PRISMA flow diagram.
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40 41 **Data extraction and management**

42 Various characteristics of the eligible studies will be extracted, including the first
43 authors' last names, year of publication, location of the study (country), study
44 design, primary objective, population, sample size, follow-up period,
45 inclusion/exclusion criteria, type of mobile application used, type of control, and
46 primary results. Standardized data extraction forms will specifically be created
47 for this review and the results will be subsequently entered into a database. All
48 data entries will be double-checked.
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56 57 **Addressing missing data**

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

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

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22 The heterogeneity between study results will be evaluated using a standard X^2
23 test with a significance level of $p < 0.1$. To assess heterogeneity, we plan to
24 compute the I^2 statistic, which is a quantitative measurement of inconsistency
25 across studies. A value of 0% indicates no heterogeneity, whereas I^2 values
26 $\geq 50\%$ indicate a substantial level of heterogeneity; however, heterogeneity will
27 be assessed only if it is appropriate to conduct a meta-analysis.
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36 **Analysis**

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38 Data will be entered into the Review Manager software (RevMan5.2.3). This
39 software allows the user to enter protocols; complete reviews; include text,
40 characteristics of the studies, comparison tables, and study data; and perform
41 meta-analyses. For dichotomous outcomes, we will extract or calculate the odds
42 ratio (OR) and 95% confidence interval (CI) for each study. In case of
43 heterogeneity ($I^2 \geq 50\%$), the random-effects model will be used to combine the
44 studies to calculate the OR and 95% CI, using the DerSimonian-Laird algorithm
45 in the meta for package, which provides functions for conducting meta-analyses
46 in R.
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56 Other study characteristics and results will be summarized narratively if the
57 meta-analysis cannot be performed for all or some of the included studies.
58 Sensitivity analyses will be used to explore the robustness of the findings
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3 regarding the study quality and sample size. This is only possible if we can
4 conduct a meta-analysis. Sensitivity analyses will be shown in a summary table.
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8 **Grading quality of evidence**

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

21
22 Non-adherence to cancer treatment is a very common and relevant clinical
23 problem, with a significant adverse impact on the healthcare system. In this
24 systematic review and meta-analysis, we aim to determine the effect of mobile
25 applications on the improvement of treatment adherence in cancer survivors. In
26 theory, mobile applications can improve adherence to anti-cancer treatment,
27 because they can remind the patient to take the medicine on time and assist in
28 care management.[27, 28] We expect that our study will provide accurate data
29 to develop effective strategies for adherence to anti-cancer treatment and help
30 to improve our understanding of the role of mobile applications in this context.
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40 **ETHICS AND DISSEMINATION**

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

51
52 Data used in this systematic review will be cited in the reference list,
53 irrespective of whether data is generated by the author(s) or by other
54 researchers. That is, data are publicly available. Findings of this systematic
55 review will be published in a peer-reviewed journal and updates will be
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3 conducted if there is enough new evidence that may cause any change in the
4 review conclusions.
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8 **Acknowledgments**

9
10 The authors acknowledge the assistance provided by the Graduate Program in
11 Health Sciences of the Federal University of Rio Grande do Norte (UFRN) in
12 conducting the literature search.
13
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15

16 **Contributors**

17
18 KSM, BS, and AKG designed this systematic review and meta-analysis. KSM
19 drafted the manuscript, and AKG revised it. KSM, RNC, and AKG developed
20 the search strategies and KSM, JFQ, and MNM will implement it. KSM, MNM,
21 JFQ, and WAC will track potential studies, extract data, and assess the quality;
22 in case of disagreement between the authors, AKG will advise on the
23 methodology and will be the referee. RNC will complete the data synthesis. All
24 authors have approved the final version of this manuscript.
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33
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35 commercial, or not-for-profit sectors.
36
37
38

39 **Competing interests**

40
41 None declared.
42
43

44 **Patient consent for publication**

45
46 Not required.
47
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Figure 1: PRISMA flow diagram.

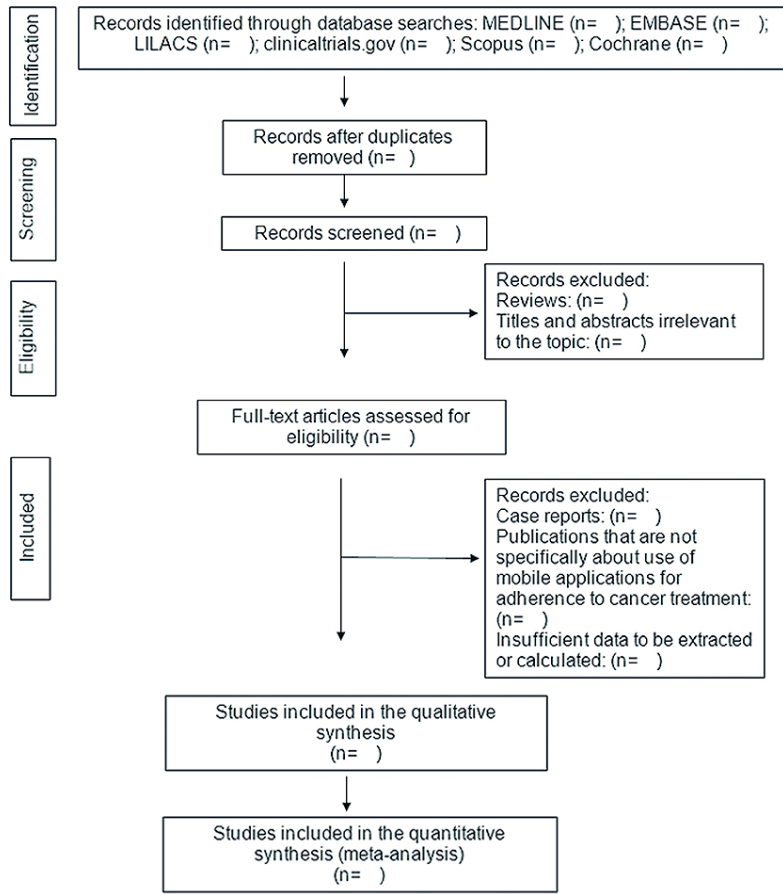


Figure 1 Flow diagram of the search for eligible studies in the use of mobile applications for adherence to cancer treatment: CENTRAL, Cochrane Central Register of Controlled Trials.

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. PRISMA Checklist

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* 2016;5:15

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					

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

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

For peer review only