

Development and Proof-of-Concept of a Smartphone Self-Management Program to Support Adherence to Oral Chemotherapy in Young and Adults with Cancer

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List of Abbreviations

AVR	Automated Voice Response System
AYA	Adolescents and young adult
CML	Chronic myeloid leukaemia
CTCAE	Common Toxicity Criteria Adverse Events
HIV	Human immunodeficiency virus
IV	Intravenous
MARS-5	Medication Adherence Report Scale
MASCC	Multinational Association of Supportive Care in Cancer
MEMS	Medication Event Monitoring System
MMAS-8	Morisky Medication Adherence Scale-8
MOATT	MASCC Oral Agents Teaching Tool
NGO	Non-profit organisations
OAD	Oral antineoplastic drugs
OC	Oral chemotherapy
SMS	Short message service
VAS	Visual Analogue Scale
WHO	World Health Organization

Contextual Statement

This thesis is submitted as a Thesis Containing Published Research in accordance with the University of South Australia's Academic Regulations for Higher Degrees by Research Clause 16.1.1.b.

Papers are presented in their published form (PDF files) except for Paper 4 (Chapter VI) which was submitted for journal's peer review and is not approved or published at the time this thesis is submitted.

Each publication was accepted by a peer-review journal recognised for the University of South Australia's publication collection (outlined below) and relevant to the discipline of psycho-oncology.

The introduction sections of the papers included in this thesis may contain evidence that is repeated across papers and chapters of this manuscript. This information was deemed essential to provide readers with an overview to each of the studies. Additionally, please note that the papers' text and referencing styles match guidelines from the publishers' journals and differ from the one used in this thesis (APA 6th edition).

Appendix A contains the signed 'Statement of Authorship' for each published, co-authored paper including the contribution of each author.

I contributed to the design of the studies in this thesis and was the main researcher responsible for literature reviews, recruitment, screening and enrolment of participants into the studies as well as data collection. I conducted all data analysis and interpretation. As first author to all papers, I wrote and submitted all manuscripts and responded to reviewer comments before re-submitting amended manuscripts. All my work was supervised by Dr. Kate M. Gunn, Professor Ian Olver, Associate Professor Pandora Patterson and Dr. Vijay Suppiah.

Appendix B contains the Publisher Copyright Permission Statement for Paper 1 in line with copyright law and intellectual property requirements. Paper 2 is an open-access article

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The reference list at the end of this thesis contains references from chapters 1, 2 (except for Paper 1), 3, 4-6 (overview of papers only) and 7, and is organised in alphabetical order.

List of Publications Arising from this Thesis

CHAPTER II:

Skrabal Ross, X., Gunn, K.M., Suppiah, V., Patterson, P. & Olver, I. (2020). A review of factors influencing non-adherence to oral antineoplastic drugs. Support Care Cancer. https://doi.org/10.1007/s00520-020-05469-y

This paper was submitted for publication in the journal Supportive Care in Cancer on 08 February 2020. The manuscript was peer-reviewed by two reviewers and accepted for publication on 13 April 2020. This journal has an impact factor of 2.754 (2018) and is ranked 8/65 (Q1) in Rehabilitation, 27/98 (Q2) in Health Care Sciences and Services, and 134/230 (Q3) in Oncology categories (Journal Citation Reports).

CHAPTER IV:

Skrabal Ross, X., Gunn, K. M., Patterson, P., & Olver, I. (2018). Mobile-Based Oral Chemotherapy Adherence-Enhancing Interventions: Scoping Review. JMIR Mhealth Uhealth, 6(12), e11724. doi:10.2196/11724

This paper was submitted for publication in the journal JMIR Mhealth and Uhealth on 29 July 2018. The manuscript was peer-reviewed by two reviewers and accepted for publication on 08 October 2018. This journal has an impact factor of 4.301 (2018) and is ranked 13/98 (Q1) in Health Care Sciences and Services and 2/26 (Q1) in Medical Informatics categories (Journal Citation Reports).

CHAPTER V:

Skrabal Ross, X., Gunn, K. M., Patterson, P., & Olver, I. (2019). Development of a Smartphone Program to Support Adherence to Oral Chemotherapy in People with Cancer. Patient preference and adherence, 13, 2207-2215. doi:10.2147/PPA.S225175

This paper was submitted for publication in the journal Patient Preference and Adherence on 07 August 2019. The manuscript was peer-reviewed by two reviewers and accepted for publication on 30 October 2019. This journal has an impact factor of 2.097

(2018) and is ranked 59/160 (Q2) in Medicine, General and Internal category (Journal Citation Reports).

Summary

Medication non-adherence is a global health issue that impacts on individual health outcomes and healthcare systems. Despite the dangerous health complications of not following oral chemotherapy (OC) prescriptions, rates of non-adherence to these medications are high (up to 54%). Although evidence on the extent to which adolescents and young adults (AYAs) adhere to OC is limited, their developmental stages may place them at a higher risk of medication non-adherence than other age groups. There are advantages in the use of OC but the lack of standardised monitoring procedures for OC adherence and related side-effects is a challenge to users and oncology healthcare teams. There is a need to provide people with cancer with strategies that support their adherence to OC prescriptions. Due to their extended availability, mobile phones are a promising tool to deliver medication adherence interventions. There is growing evidence on the positive effects of Short Message Service (SMS) interventions on adherence to medication for chronic diseases. However, it is not clear whether these types of interventions are effective in supporting adherence to OC. This research aimed to examine the proof-of-concept of a smartphone self-management program to support adherence to OC in AYA and adult people with cancer.

The first step in the development of the smartphone self-management program was to identify the main modifiable reasons for OC non-adherence and behavioural-change strategies that show promise in improving these factors. Literature reviews led to three main reasons for OC non-adherence (forgetfulness, side-effects, and poor knowledge about OC) and three behavioural-change strategies to improve those factors: medication-taking reminders, information about the management of OC side-effects, and information about OC.

The next step involved a formative qualitative study with nine OC users (two AYA, 20 years old; seven adults, 50-71 years old; 72% female). Thematic Analysis of semi-structured interviews with the participants allowed to identify common preferences on features of the program, for example, the use of one-way, short and text-based SMS

medication-taking reminders, personalised with the name of the recipient and delivered shortly before OC was due.

The third step in the development of the program consisted of a scoping review to explore what was known about the available mobile phone-based interventions to increase adherence to OC, the utility of those interventions in increasing adherence to OC and knowledge gaps that could be addressed by a novel mobile phone-based program. A lack of mobile phone-based interventions to increase adherence to OC was observed. None of the interventions were delivered exclusively via SMS platforms and those with SMS components did not include strategies to address the three main modifiable reasons for non-adherence to OC that were identified in this research. Additionally, none of the studies involved AYA with cancer.

The previously described research steps led to the development of a novel smartphone self-management tool to support AYA and adults' adherence to OC.

A non-randomised, proof-of-concept trial of the smartphone self-management program was conducted at six Australian hospitals. Twenty-two participants (17-74 y/o) with a median age of 60 years and 52% female, were recruited into the study and 21 of them completed post-intervention assessment (week 10). High acceptability (95%) and satisfaction (81%) with the program were found. Adherence to OC (assessed by the self-report tool MARS-5 and the Medication Event Monitoring System) was not found to increase with the use of the program. An increase in OC knowledge was found at post-intervention ($p=0.010$).

In summary, the development and trial of the novel smartphone self-management program described in this thesis, contribute to addressing the lack of mobile phone interventions to improve non-adherence to OC in AYA and adults with cancer and knowledge gaps from the available tools. The program showed high satisfaction and acceptability from users and its trial highlighted relevant intervention and methodological modifications that need to be considered before a larger randomised controlled trial of the program is conducted.

Declaration by Author

I declare that:

this thesis presents work carried out by myself and does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; to the best of my knowledge it does not contain any materials previously published or written by another person except where due reference is made in the text; and all substantive contributions by others to the work presented, including jointly authored publications, is acknowledged.



Xiomara Skrabal Ross 14 July 2020

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CHAPTER I. Introduction

1.1. Oral Chemotherapy Use. Advantages and Challenges

For several decades cancer chemotherapy agents have been mainly administered intravenously. Although some of the oral chemotherapy (OC) drugs (e.g. cyclophosphamide, methotrexate, chlorambucil, 6-mercaptopurine) have been available to patients for many decades, it was the approval of the drug capecitabine, in 1998, which marked the beginning of a new era when numerous novel oral agents started being approved, including innovative targeted drugs (imatinib, gefitinib and erlotinib) (Weingart et al., 2008). The availability and use of oral antineoplastic drugs (OAD) have increased considerably in the last two decades, and it is estimated that 25% of these drugs (approved and in the process of approval) are intended for oral administration. This figure is expected to increase in the coming years (Weingart et al., 2008).

OC drugs can be divided into three types: oral versions of the same intravenous (IV) drug (e.g. methotrexate, etoposide), oral versions of IV molecules of the same class (e.g. idarubicin, temozolomide), and targeted therapy available only in an oral dosage form (imatinib, sorafenib) (Banna et al., 2010). In the first two cases, a choice can be made by physicians on the form of drug administration (IV or oral) that is more appropriate for patients based on individual profiles. In the third case, a choice is not possible and in some diseases (e.g. chronic myeloid leukaemia) oral targeted chemotherapy is the first-line treatment. Regardless of the nature of OAD, the term “chemotherapy” is commonly used to embrace all cytotoxic and targeted biological drugs used in the treatment of cancer (Weingart et al., 2008). In addition, patients diagnosed with some cancer types (e.g. breast cancer) may be prescribed oral hormonal therapy (also referred to as endocrine therapy). These drugs do not fit into the concept of OC previously described, but research on adherence to OAD frequently incorporates both, hormonal and non-hormonal therapy. Hormonal therapy can be classified into two groups: drugs that inhibit the production of hormones involved in cancer growth

and therapies that aim to change how certain hormones behave (Cancer Australia, 2019).

OC is preferred by most patients over conventional IV chemotherapy. This is due to the convenience of taking the drug at home, avoidance of separation from family and work, increased sense of independence by being responsible for treatment administration, avoidance of invasive needles for IV treatment, and better quality of life (Bedell, 2003; Tadic, Spasojevic, Tomasevic, & Dejanovic, 2015). However, patients' preference for OC may be contingent upon its efficacy. For example, in a survey of 103 palliative cancer patients, 92 (89.3%) of them expressed a preference for oral versus IV chemotherapy due to convenience, previous problems with IV access or needles, and preference for a better OC intake environment outside of the hospital. This preference was based on achieving similar health outcomes with the oral version of the drug, which means that they were not willing to take the oral version if the response rate was lower (70% of participants) or shorter (74% of participants) than with IV drug formulations (Liu, Franssen, Fitch, & Warner, 1997).

Despite the previously described advantages, patients prescribed OC face the challenge of self-managing complex drug regimens under limited professional supervision outside of hospital settings. Three of the main challenges of OC treatments are monitoring of drug-related symptoms/side-effects, patient safety, and adherence (Weingart et al., 2008). Although most of the OC and IV chemotherapy-related side-effects are similar (Spoelstra et al., 2013), the unique mechanism of action of some oral agents (e.g. targeted therapies) and potential for medication errors (e.g. patients take a higher dose than prescribed) may lead to different toxicity profiles compared to IV drugs (Goodin, 2007). Some of these adverse effects can be severe and require close monitoring from the treating team. For example, erlotinib can cause a rash that in some cases can be extremely uncomfortable, resulting in discontinuation of the therapy. There may also be variable bioavailability (the degree and rate at which the drug is absorbed by the body's circulatory system) of oral drugs. Interaction with prescription and non-prescription drugs, food and herbal supplements is another challenge in

the use of OC. Some drugs should not be taken with food, especially food with high fat content (e.g. sorafenib) because it can reduce the absorption and hence the bioavailability of the drug. On the other hand, other agents need to be taken with food (e.g. imatinib) to avoid gastro-intestinal irritation (Aisner, 2007).

Oncology services and practices are organized around IV chemotherapy delivery, which encompasses strict monitoring and administration procedures (Banna et al., 2010). However, in the context of a growing trend in the use of OC, most health institutions do not have adequate standardized practices in medication adherence and side-effect monitoring, safety, and education to support adequate patients' self-administration of OC (Weingart et al., 2012)

1.2. Adherence to Oral Chemotherapy

1.2.1. Medication Adherence.

Medication adherence is considered a crucial element in the management of chronic diseases in general, yet it is estimated that in developed countries approximately 50% of chronically-ill patients fail to take their drugs as prescribed (Sabaté, 2003). Medication non-adherence has been associated with poorer outcomes, increased use of healthcare resources including more visits to clinicians and more frequent and longer hospitalizations (Thompson, Dewar, Fahey, & McCowan, 2007).

The impact of non-adherence to treatment transcends the individual and generates a burden on healthcare systems, with yearly estimates of the cost totalling $100 billion for North America (Chisholm-Burns & Spivey, 2012) and $380 million in Australia (Australian Council for Safety and Quality in Health Care, 2002). A recent study found that the economic impact of non-adherence to medications on healthcare systems was dramatically higher in cancer (up to US$ 150,000 per person, per year) compared to 13 chronic diseases, with non-adherence to medication for Parkinson's disease representing the second-highest economic impact (up to US$ 52,023 per person, per year) (Cutler, Fernandez-Llimos, Frommer,

Benrimoj, & Garcia-Cardenas, 2018).

The term “adherence” was recently adopted in literature to replace the term “compliance” because the former is considered less judgemental and recognizes the active role of patients in their therapeutic process. Adherence is defined in several studies as “the extent to which patients take medications as prescribed by their health providers”(Osterberg & Blaschke, 2005).

This definition emphasizes a unidirectional instruction given by doctors and places patients in a passive position as direction-followers. In the light of advances in healthcare systems towards recognising patients as decision-makers and active agents in managing their chronic illnesses, the World Health Organization (WHO) conceptualized adherence as “the extent to which a person’s medication-taking behaviour, following a diet and/or executing lifestyle changes corresponds with agreed recommendations of a healthcare provider” (Sabaté, 2003).

Medication non-adherence can manifest in different ways, allowing categorization into three main types: primary or non-fulfilment in which the medication is prescribed but the patient never fills or initiates the prescription, non-persistence or the patients’ discontinuation of a prescribed drug after it is started, and non-conforming, in which drug intake does not correspond with the doctor’s prescription (e.g. skip doses, overdose) (Jimmy & Jose, 2011). The current research is focused on the last category, non-conforming, and the term “non-adherence” is used throughout this thesis to refer to a drug intake that does not correspond with that agreed between patient and health professional.

1.2.2. Adherence measure tools.

According to the WHO, the use of reliable adherence assessment is necessary to determine the efficacy of treatment plans and ensure that changes in patients’ clinical outcomes can be attributed to the treatment (Sabaté, 2003). Currently, there is no gold-standard operational definition or measure of medication adherence. Despite this lack of ideal

definitions and measures, some trends are evidenced in adherence-focused research. Measures collect information about one or multiple dimensions of adherence behaviour involved in the differentiation between poor and optimal adherence (taking medications as prescribed, at the exact time, dose, and length of treatment) (Breccia, Efficace, & Alimena, 2011). The most commonly accepted operational definition of medication adherence in chronic diseases is based on adherence rates, which are the number of doses taken over the number of prescribed doses, with a cut-off of ≥ 80% to be considered adherent (Verbrugghe, Verhaeghe, Lauwaert, Beeckman, & Van Hecke, 2013). In the context of OC adherence, the situation is like that of other chronic illnesses. In a recent study that evaluated the effect of a mobile app intervention on adherence to OC, adherence was defined as the percentage of prescribed doses taken during 12 weeks, as measured by the medication event monitoring system (MEMS), with a cut-off rate of >80% (Greer et al., 2017). Disparities in the operational definition of OC adherence are also evident in the literature. In a systematic review of 25 journal articles addressing determinants of adherence or persistence to OAD in adults, the studies' definition of non-adherence cut-off rates varied between <80%, 90% and 100% or more (110%) of the prescribed drugs (Verbrugghe et al., 2013).

Tools to measure medication adherence are classified into direct and indirect methods. Direct methods include measures of drug (or its metabolites) concentration in blood or urine and in-blood detection of biological markers. These methods are objective, which is an advantage over other types of strategies, yet they can be expensive and demanding for healthcare professionals (Osterberg & Blaschke, 2005). In some cases, results may be altered by individual variations in metabolism (diet, absorption, rate of excretion) (Vitolins, Rand, Rapp, Ribisl, & Sevick, 2000).

Indirect methods consist of self-report (questionnaires, diary, interviews), pill-count, pharmacy rates of prescription re-filling, MEMS, and assessment of clinical response. Self-report tools are the most commonly employed medication adherence assessment strategies.

These tools are easy to use in oncology practices but they may overestimate adherence because patients modify their responses to meet the social expectations of the treating team. For example, in a systematic review of eight journal articles on adherence to OAD, three of the studies found that adherence scores gathered via self-report questionnaires were higher than those of MEMS and pill count (Atkinson et al., 2016). With the evolution and penetration of mobile technology, new real-time adherence self-report strategies have been designed which could generate opportunities for treating teams to act upon poor medication adherence in real-time (Rasschaert et al., 2016).

A number of validated self-report tools have been used to assess OC and oral hormonal therapy adherence. These are the Morisky Medication Adherence Scale-8 (MMAS-8), the Visual Analog Rating Scale (VAS), and the Medication Adherence Report Scale (MARS-5). To identify the most suitable self-report tool for the current research, the structure, advantages, and disadvantages of each tool were considered and a description is offered in the next paragraphs.

MMAS-8: the MMAS-8 (Morisky, Ang, Krousel-Wood, & Ward, 2008), consists of eight close-ended questions about medication intake behaviours with dichotomous responses (yes or no) and a five-point Likert response for the last item. This tool has shown good pooled internal consistency in type-2 diabetes ($\alpha = 0.67$) and osteoporosis ($\alpha = 0.77$). However, the validity of MMAS-8 may not be high, as it previously was shown to lack specificity and sensitivity (Moon, Lee, Hwang, Hong, & Morisky, 2017). The MMAS and its variations have been extensively used in studies on diverse chronic diseases in many countries (Unni & Farris, 2015). The MMAS-8 has also been used to measure adherence to OC (Efficace et al., 2012; Jönsson, Olsson, Söderberg, & Wadenvik, 2012; Kekale, Soderlund, Koskenvesa, Talvensaari, & Airaksinen, 2016; Sommers, Miller, & Berry, 2012). One of the disadvantages of this tool is that it collects information about a small number of reasons for medication non-adherence and does not perform an extended assessment of medication adherence which

makes it difficult to build interventions based on the results (Unni & Farris, 2015). Additionally, the MMAS-8 is not free for researchers to use.

VAS: the VAS (Giordano, Guzman, Clark, Charlebois, & Bangsberg, 2004), is a single-item visual analogue scale that asks patients to identify, in a continuum from 0%-100%, the percentage of medication they took in the past month. It showed a high correlation ($r = 0.76$) with unannounced pill count in a study of adherence to antiretroviral therapy in human immunodeficiency virus (HIV) patients (Giordano et al., 2004). This scale is suited to assess continuous behaviours (e.g. pain, symptoms) and allows participants to freely express their options instead of having to choose from restricted categories (Klimek et al., 2017). However, participants may also find difficult to determine the point in the scale that best represents their behaviour and due to the nature of the VAS, which requires subsequent distance measures, data entry for statistical analysis encompasses a larger effort and high costs (Klimek et al., 2017). This issue of statistical analysis seems to be improved by the computer-based version of the VAS. This scale only provides information on the estimated rates of medication adherence and does not contemplate the reasons behind non-adherence behaviour. The VAS has been used to assess adherence to OC and oral hormonal therapy in previous studies (Brier et al., 2015; Gebbia et al., 2013; Mazzeo et al., 2011; Noens et al., 2009) and it is available for free use.

MARS-5: the MARS-5 (Horne, Hankins, & Jenkins, 2001) is a variation of the original MARS created to assess adherence to psychosis treatment (Thomson et al. 2000). The design of the original tool aimed to build upon limitations in the use of the MMAS-8 and the Drug Attitude Inventory. The MARS-5 consists of five items related to medication non-adherence behaviour. Patients score their behaviour based on the frequency of each item (always, often, sometimes, rarely and never). Items are individually scored from one (always) to five (never), adding to up to 25 points which indicate higher medication adherence. This tool provides information on whether non-adherence is related to forgetfulness, intentional

interruption, dose changes, or omission. MARS-5 is available free for use in research.

The MARS-5 authors estimated that the reliability coefficient for this tool was α= 0.83, based on a sample of patients diagnosed with HIV, Crohn's disease, diabetes, asthma, and ulcerative colitis (Horne et al., 2001). This scale also demonstrated good internal and test-retest reliability when used in patients with chronic diseases and showed a good correlation with the dosage unit count method (Bhattacharya, Easthall, Willoughby, Small, & Watson, 2012). In MARS-5 adherence is frequently defined as a score of 25 points on the scale, which is the maximum score. This definition is relevant in light of recent evidence that when lowering the cut-off to 20 points, MARS-5 was not able to reach enough sensitivity and specificity to detect non-adherers to chronic obstructive pulmonary medication, compared to dichotomized measures of medication refill (Tommelein, Mehuys, Van Tongelen, Brusselle, & Boussery, 2014). In addition to its use in chronic disease research, the MARS-5 has also been utilized to measure adherence to OAD. In a study of adherence to tamoxifen in breast cancer patients, MARS-5 showed internal consistency of α= 0.68 and high correlation (r= 0.049, $p < 0.001$) with a single-item questionnaire used as an additional adherence measure (Grunfeld, Hunter, Sikka, & Mittal, 2005). Another study with 62 patients diagnosed with non-small cell lung cancer measured adherence to erlotinib with the MEMS and the MARS-5. High adherence to erlotinib was found with both measures (mean MEMS 96.8 % ± 4.0, mean MARS-5 24.9 ± 0.4). Sub-optimal adherence, defined in this study as <25 points in MARS-5 was associated with sub-optimal time-points of a meal (OR 4.83, p= 0.042) which is considered a feature of non-adherence to erlotinib (Timmers et al., 2015). Another example of the use of MARS-5 in the OC context is a study with 43 breast and colorectal cancer patients prescribed capecitabine. This study aimed to determine the magnitude of non-adherence and the factors that impact on capecitabine intake behaviour. Findings showed that 23.3% of the participants were non-adherent to capecitabine (MARS-5 < 25 points) mainly due to forgetfulness (Bhattacharya et al., 2012).

Although all self-report scales may tend to overestimate medication adherence when compared to other assessment methods, they are practical to implement in clinical settings, provide a good description of adherence behaviour, and offer a comparison point with other assessment tools used in adherence research. The MARS-5 is a brief scale that is easy to administer and interpret. It captures different expressions of medication non-adherence (omission, dose change, interruption) and forgetfulness as a reason for non-adherence. The information collected by this tool is aligned with the aims of the current research and it has been successfully used in OC studies, showing convergent validity with other adherence assessment tools (Bhattacharya et al., 2012).

The second commonly used strategy to measure adherence, other than patient self-report, is pill count (counting the number of pills remaining in the drug bottle at a medical visit). This strategy may also be influenced by patients' perception of social desirability because patients may discard the content of the bottle to appear adherent. Additionally, errors from manual medication counts may produce inaccurate results (Osterberg & Blaschke, 2005). Rates of pharmacy prescription re-filling can be a more accurate measure of adherence if they are assessed at several time-points. This strategy is also helpful to compare results from self-report tools. However, the fact that patients re-fill their medications does not always imply correct intake (Osterberg & Blaschke, 2005).

Although the previously described strategies are commonly used in clinical practice, none of them provide additional information on adherence behaviour, such as the timing of medication. Electronic monitors such as the MEMS (the most commonly used electronic monitor) consist of a pill bottle with a cap that contains a microelectronic chip and tracks the date and time the medication is taken (see Figure 1). This is the most accurate strategy, yet it is still an indirect tool because patients may open the bottle and not take the medication or take more pills than prescribed. In terms of the distinction between adherent and non-adherent patients, the most common cut-off in studies using MEMS is in line with the most common

operational definition of adherence that was described at the beginning of this section (≥ 80%). Therefore patients who open the MEMS cap 80% or more times (based on the prescribed doses) are considered adherent to their medication while those patients who open the cap less than 80% of the time are categorized as non-adherent (Nguyen, La Caze, & Cottrell, 2014). It is important to consider that in the case of OC agents, with the exemption of imatinib in chronic myeloid leukaemia (CML) (≥ 90%) (Marin et al., 2010) and tamoxifen in breast cancer (≥ 80%) (McCowan, Wang, Thompson, Makubate, & Petrie, 2013), there is a lack of evidence on the ideal adherence cut-off rates required to achieve optimal clinical outcomes in cancer patients.

The cut-off rate of 80% seems to be the only consistent measure used by researchers when analysing medication adherence data from MEMS. However, a lack of standard measures and methods to summarize adherence data from MEMS was recently described in a systematic review (Hartman, Lems, & Boers, 2018).

Figure 1

MEMS devices



MEMS is also frequently used as a standard for validation of other adherence measurement tools, especially self-report tools (Lam & Fresco, 2015). When compared to MEMS, a number of adherence measures have shown to overestimate medication adherence. A scoping review of 117 studies found that self-report tools overestimate adherence by 17%

while pill count surpasses MEMS scores by 6% (El Alili, Vrijens, Demonceau, Evers, & Hiligsmann, 2016). Another example is a comparison study between MEMS and a self-report questionnaire in 416 children and AYAs (0-21 y/o) in maintenance treatment with 6-mercaptopurine for acute lymphocytic leukaemia. This study found that a single-question self-report tool overestimated adherence to the drug (at least sometimes) in most of the participants (84.4%), compared to data gathered through MEMS. Only 12% of the participants showed a perfect match between the self-report and MEMS adherence scores (Landier et al., 2017).

MEMS is considered one of the most reliable indirect adherence measures but its use is not without drawbacks. The bulky size of the bottles may make it uncomfortable to carry the drug to work or out of the house (Deschamps et al., 2004). Moreover, the efficacy of some drugs may be compromised if taken out of the original blister packs to fill the MEMS bottle (Church & Smith, 2006). This issue can be solved by cutting individual pills within the original blister packs and then placing them into MEMS bottles. MEMS can be costly and is more commonly used in clinical trials and research than in clinical practice (Osterberg & Blaschke, 2005). From a research perspective, one of the challenges associated with the use of MEMS is the difficulty in coordinating medication refills with outpatient pharmacies as some patients may leave the MEMS at home when refills are due, making it impossible to fill the devices at the right time (Diaz et al., 2001). High costs and resources are also implicated in patient education regarding the correct use of the MEMS. Education is relevant since incorrect use of the MEMS affects adherence measures (Diaz et al., 2001).

Given that all the previously reviewed methods show limitations in assessing medication adherence, the best-recommended practice consists of selecting a combination of adherence measure strategies (e.g. MEMS and a self-report tool) in-line with the objectives of the research (Osterberg & Blaschke, 2005).

1.2.3. Adherence to oral chemotherapy.

Adherence to OC is one of the main determinants of the efficacy of OC and patients' survival rates; failure to adhere can lead to higher toxicity, complications, relapse, hospitalizations, and death (Thompson et al., 2007).

Evidence on rates of adherence to OC presents wide variations across the literature, depending on the study sample, methods, drug and cancer type, follow up periods, adherence measure tools, and adherence cut-off used (Greer et al., 2016). A literature review that included 19 studies on OAD adherence of patients with various cancer types, found adherence rates ranging from 69% to 100%. OC adherence rates across 6-month follow-up periods ranged from 69% to 100% and were lower at one-year follow-up (varying between 69.6% and 88.2%). Poor adherence rates also differed according to the measurement strategies used, finding baseline non-adherence of 20.5% with MEMS and 36.1% according to physician report. Assessment through medication possession ratio at one year showed poor adherence rates from 27.3% to 40.9% in the reviewed studies (Greer et al., 2016).

In CML, an alarming proportion of non-adherent patients to tyrosine kinase inhibitors (e.g. imatinib) (20.7%) was found in a sample of 2456 patients across 63 countries. Findings from this study also showed that less than half of the patients were perfectly adherent to their OC (32.7%) with even lower proportions of adherent patients found in Anglo-American (24.2%) and African (19.1%) countries as assessed by the self-report tool MMAS-8 (Geissler et al., 2017).

Adherence to oral chemotherapy in AYA.

The age definition of AYA is not consistent across nations, states, or studies and varies from as young as 12 to 39 years old. In this thesis, the definition of AYA used by the Australian Youth Cancer Service was adopted; 15-25 years old (CanTeen Australia, 2017).

During the AYA years, individuals experience dramatic psychological, physiological, and social changes in their developmental process (Zebrack, Santacroce, Patterson, & Gubin,

2016). This is a time for establishing independence from parents, focusing on career and life goals, engaging in significant peer and romantic relationships, exploring sexuality and developing identity, and personal value systems (Havighurst, 1972; Schwartz & Parisi, 2013; Zebrack et al., 2016).

Cancer diagnosis and treatment have a negative impact on AYA's developmental process. For example, during cancer treatment, peer relations may be affected or lost, parental relationships step back from their evolution towards independence to become a more dependent relation, and sexual exploration may be delayed. The undesired side-effects from cancer treatment (e.g. hair and weight loss) have an adverse impact on AYA's development of identity and self-image, making it complicated for them to self-manage these side-effects and adhere to OAD prescriptions (Butow et al., 2010).

Impulse control, recognition of consequences, and emotional responses to stressful stimuli are physiologically underdeveloped in AYA (Zebrack et al., 2016). Due to the developmental challenges of this age group, they may be at a higher risk of cancer medication non-adherence (Zebrack et al., 2016). For instance, the tendency to engage in risk-taking behaviour may result in poor adherence. While AYAs tend to be able to recognize the immediate consequences of their behaviour, they are often unwilling or unable to identify the impact of long-term consequences (Nevins, 2002). Therefore, if non-adherence to treatment does not produce evident and immediate consequences, AYAs might be likely to repeat the risky behaviour.

AYA's sense of independence and ownership of their body and health should be acknowledged by cancer support strategies provided to this population (Kim, Patterson, & White, 2018), including medication adherence interventions.

OC non-adherence rates between 25% and 53% have been identified by a small number of studies with oncology AYAs treated with mercaptopurine (Lau, Matsui, Greenberg, & Koren, 1998; Pai, Drotar, & Kodish, 2008; Wu et al., 2018), imatinib (Ganesan

et al., 2011; Unnikrishnan et al., 2016) and methotrexate (Wu et al., 2018). However, this body of knowledge presents variations in the definition of AYA ages, adherence measures, and cut-off rates, which makes it difficult to generalize findings.

The lack of evidence on adherence to OC in AYA is attributed to their traditional inclusion into paediatric or adult samples. The recent acknowledgment of AYA as a group provides the opportunity to focus research on this population and accumulate evidence. The broader body of knowledge about this topic focuses on cancer medication regimens in general, involving non-OC drugs (e.g. prednisone, a steroid and penicillin, an antibiotic), IV drugs, radiotherapy, and even attendance to treatment appointments. The results of most of the available investigations do not differentiate between adherence to OC and other medications used in cancer treatment. In this context, rates of non-adherence to cancer treatment regimens in AYA vary from 27% to 63% (Hullmann, Brumley, & Schwartz, 2015; Kondryn, Edmondson, Hill, & Eden, 2011). In chronic diseases, low rates of adherence to medication have been found in the AYA group (62.3% in HIV with 12-24y/o; 23% in asthma, epilepsy, diabetes mellitus and rheumatoid arthritis with 13-17y/o and 22% in epilepsy with 13-17y/o) (Kim, Gerver, Fidler, & Ward, 2014; Kyngas, 2000a, 2000b). A low median adherence rate of 43% was also found amongst adolescents (15-18 y/o) on corticosteroid treatment for asthma (Naimi et al., 2009).

A recent systematic review also highlighted the risk of increased poor clinical outcomes (death, fever, infection, low molecular response) in AYA (15-39 y/o) who do not adhere to their OAD prescriptions (McGrady & Pai, 2019).

Despite evidence on non-adherence to OC drugs in AYA being limited in number and drug types, this group also seems to show low adherence to medication in chronic diseases and the specific characteristics and developmental stages of this age group may place them at a higher risk of medication non-adherence than children and older adults. For these reasons, it is relevant to provide AYAs with self-management strategies that support their OC intake.

Cancer patients prescribed OC face the challenge of medication self-administration under limited hospital supervision and a high number of adults and AYAs are at risk of OC non-adherence. Therefore, it is necessary to provide patients with tools to support their OC adherence outside of hospital settings.

1.3. Use of Mobile Phones to Deliver Medication Adherence-Enhancing Interventions

Due to their extensive availability, mobile phones are increasingly being used to support a number of healthcare activities such as health monitoring and promotion, telehealth, and collection and report of data (Abaza & Marschollek, 2017). The use of mobile technology (including mobile phones) in healthcare is commonly referred to in the literature as "mHealth". mHealth studies have been conducted mainly in developed countries, with the United States leading the way, and the Middle East and South America at the bottom with the least number of studies in this area (Abaza & Marschollek, 2017). In less developed countries, mobile phone social apps (e.g. Whatsapp) are used by clinicians to communicate with their patients, to send images of test results and provide short medical advice in real-time and as a telecommunication tool between healthcare professionals (Giordano et al., 2017).

Mobile platforms used in medication adherence in chronic diseases, in general, have been categorized in four groups: short message service (SMS), phone combined with an app or software, phone combined with a specific device (e.g. medical device connected to a phone via a cord) and phone combined with a wireless device (Hamine, Gerth-Guyette, Faulx, Green, & Ginsburg, 2015). A systematic review of 107 research articles published between 2003-2014, on the effect of mHealth tools on adherence to management (not medication adherence exclusively) of chronic diseases (diabetes mellitus, cardiovascular diseases, and chronic lung diseases), identified that the most commonly used delivery platform was SMS (40.2%, 43/107). SMS was used to facilitate patient-healthcare team communication, sending medication reminders, collecting data, and educating and motivating patients. Although SMS has the potential to be used in combination with other strategies, all of these studies (40.2%)

used SMS only. The second most utilized mHealth tool was smartphone apps (23.4%, 25/107) installed on patients' mobile phones to remind them to check symptoms, keep a food diary, or communicate with educators in real-time (Hamine et al., 2015). These studies were mainly conducted in the United States 34.6% (37/107), followed by the United Kingdom 10.3% (11/107) and the same number in South Korea, with only one study in India, China, and Africa. Amongst the 107 studies included in this systematic review, 27 were randomised controlled trials (RCTs) that evaluated the effect of the interventions on adherence behaviours and 15 (56%) of these studies reported a statistically significant effect on the outcome variable. Nine out of the fifteen studies reported on interventions with medication adherence as an outcome measure. Table 1 offers a description of the interventions and mobile platforms used in these studies.

TABLE 1

Intervention features in effective medication adherence interventions in chronic diseases. Extracted from (Hamine et al., 2015)

Authors	Mobile phone platform	Intervention
(Khonsari et al., 2015)	SMS	SMS reminders before intake of cardiac medications for eight weeks
(Quilici et al., 2013)	SMS	Personalized, daily SMS medication reminder
(Lv et al., 2012)	SMS	SMS reminders, two times a day asthma management plus asthma education.
(Petrie et al., 2012)	SMS	18-week tailored SMS that aimed to modify disease and medication beliefs associated with non-adherence to preventer medication.
(Strandbygaard, Thomsen, & Backer, 2010)	SMS	Daily SMS reminders to take asthma medication.
(Park, Howie-Esquivel, Chung, & Dracup, 2014)	SMS and MEMS	Intervention group one: SMS with educational messages, intervention group two: SMS with medication reminders and educational messages
(Park et al., 2015)	SMS and MEMS	Intervention group one: SMS with educational messages, intervention group two: SMS with medication reminders and educational messages
(Franklin, Waller, Pagliari, & Greene, 2006)	SMS integrated into a software system	Daily SMS (delivered via software), with goal prompts, tips and reminders tailored to participants
(Brath et al., 2013)	Electronic medication blister pack connected with mobile phones gateway and SMS	Electronic medication blister pack integrated with a mobile phone gateway that sent medication intake information to the research team. SMS reminders were sent to participants based on the information received from their mobile phones.

As it can be observed in Table 1, all of the interventions that were shown to be effective in increasing medication adherence in chronic diseases were delivered via SMS or integrated SMS into other platforms (e.g. mobile phone gateway) and 8/9 of the interventions sent medication intake reminders to chronically-ill patients. Additional intervention features in these studies included the provision of education, messages to counteract maladaptive medication beliefs, and the use of medication electronic devices such as MEMS and electronic medication blister.

A more recent systematic review (Palmer, Barnard, Perel, & Free, 2018), found that current evidence on the effectiveness of mobile-based interventions to increase medication adherence in patients with chronic cardiovascular diseases is of low-quality due to the high risk of bias and does not allow wide recommendation of their use to support medication adherence in this population. However, in light of the great potential of mobile phone platforms to support medication adherence, the authors expect future research to contribute to make clear the utility of these types of interventions in helping patients diagnosed with cardiovascular diseases in following advice on medication taking as written on prescriptions. This review included four RCTs with 2429 participants and evidence was analysed based on the effect of interventions on objective clinical outcomes (cholesterol and blood pressure) and not on medication adherence.

In the case of AYA diagnosed with chronic diseases, a recent systematic review identified 15 original research studies published between 1995 and 2015 targeting medication adherence in young patients (12-24 y/o) which delivered interventions via SMS or mobile phone apps. Seven out of fifteen (47%) studies reported statistically significant differences in medication adherence with most of the studies being of low to moderate quality (Badawy et al., 2017). SMS was the delivery platform in all the seven interventions that were found to be effective in increasing medication adherence in chronic diseases (sickle cell disease, HIV, diabetes mellitus, asthma, and liver transplant).

In chronic diseases, the use of SMS interventions seems to approximately double the odds (odds ratio) for medication adherence, as it was found in a literature meta-analysis that included 16 RCTs (Thakkar et al., 2016). The features of SMS used in the interventions were heterogeneous: five out of sixteen used personalization, half of them used bi-directional communication, and half of them used daily delivery frequency. The authors state that more research on the features or active ingredients of SMS interventions that improve medication adherence is needed.

The advantages of the use of SMS in health interventions include: the cost-effectiveness (achieving results and reaching large groups at a low cost per participant), the high penetration of SMS as worldwide, it is the most common mobile phone communication tool with three-quarters of all mobile owners using text messages, and the ability to incorporate characteristics of effective health communication interventions (tailoring, personalization, interactivity) (Hall, Cole-Lewis, & Bernhardt, 2015). In Australia, 94% of the respondents of a survey, expressed that they read SMS, which is consistent with combined results found in other countries (UK, Spain, France, and Ireland). Seventy-eight percent of these respondents stated that they would open every message they received while 16% would only open SMS from a recognized source. This last rate increases in young people (18-24 y/o) to 25%. Evidence suggests that SMS interventions have the potential to reach a high number of participants and also that making the source of the message recognizable (e.g. sender ID) may increase that number (Lam, 2018).

In the context of OC, there is limited evidence on the effectiveness of mobile phone-based interventions in supporting medication adherence. This evidence is critically reviewed in Chapter IV of this thesis. However, the success of these interventions (especially those delivered via SMS) in other chronic diseases, highlights the need for future investigation that is focused on OC adherence.

1.4. Research Aims and Questions

The primary objective of this research is to examine the proof-of-concept of a smartphone self-management program to support adherence to OC in AYA and adult cancer patients. In doing so, the following key questions will be addressed:

What are users' levels of acceptability of a smartphone program to support adherence to OC?

What are users' levels of satisfaction with a smartphone program to support adherence to OC?

We anticipate that the program will have high levels of acceptability and satisfaction amongst OC users.

More specifically, the aims of this research included:

To summarize available evidence on the main reasons for OC non-adherence and explore the impact, available interventions, and assessment methods for the main modifiable factors.

To determine the preferences AYA and adult cancer patients have about the structure and features of a smartphone self-management program that aims to support adherence to OC.

To explore what is already known about available mobile phone-delivered interventions to support OC adherence, their utility in increasing OC adherence, and to identify opportunities for future research.

To design a smartphone self-management program to support adherence to OC in AYA and adults with cancer, based on end-users' preferences, healthcare professionals' recommendations, and evidence-based strategies.

To explore proof-of-concept (acceptability and satisfaction) of the smartphone self-management program with AYA and adults with cancer.

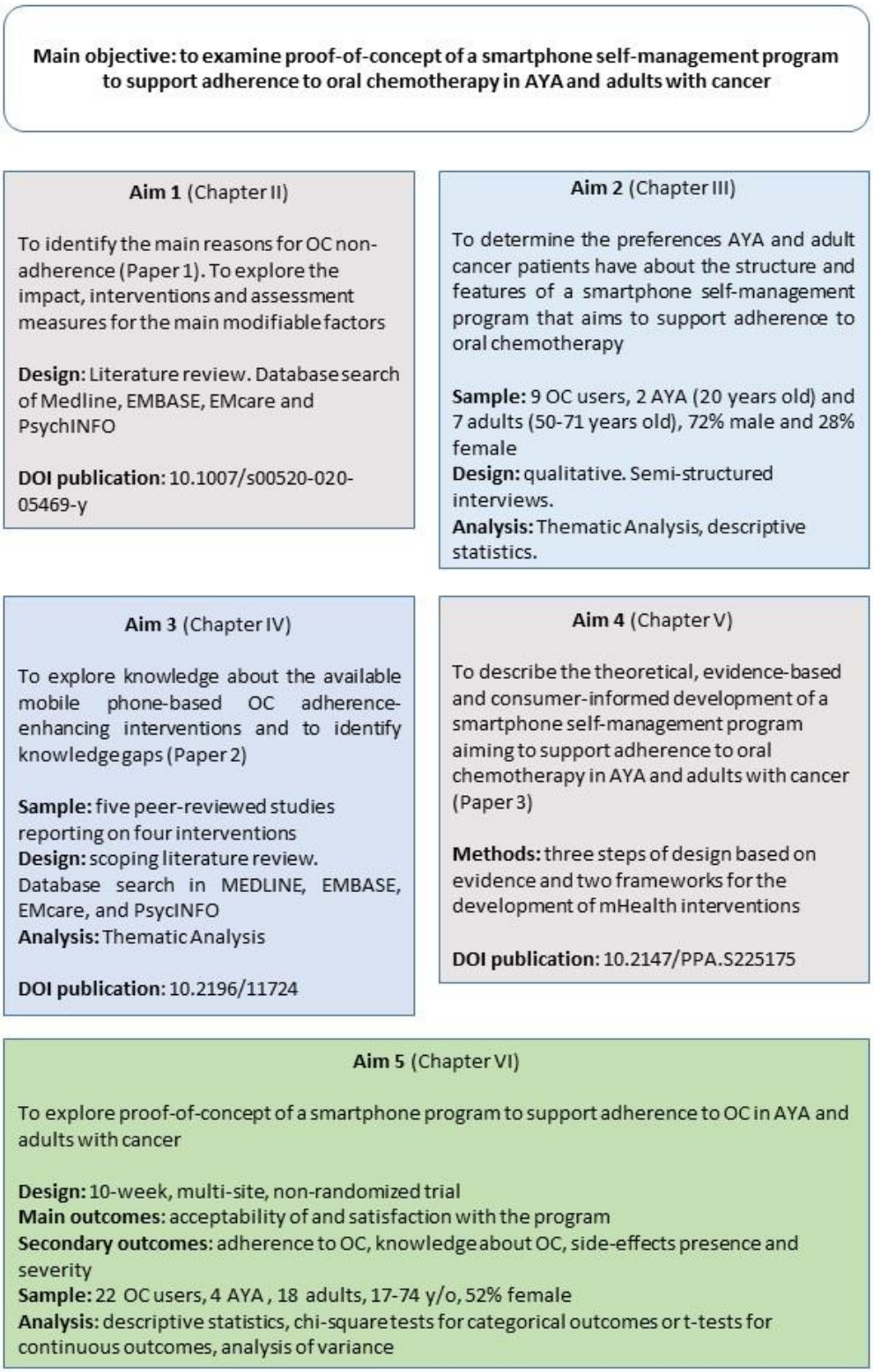
1.5. Thesis Structure

This thesis consists of seven chapters (including three publications and one manuscript

currently under review in a high-impact, peer-reviewed journal) plus 16 appendices. Chapter I sets out the background to the study, objectives, and the structure of the thesis. Chapter II presents the paper: "A Review of Factors Influencing Non-Adherence to Oral Anti-Neoplastic Drugs", followed by a detailed analysis of the evidence on the main identified factors, which are susceptible to being modified by a self-management program, available evidence-based strategies to positively modify these factors and assessment tools utilized to measure the variables. Chapter III presents a qualitative study designed to explore the preferences of AYA and adults with cancer on the structure and features of a self-management program that aims to increase adherence to OC. Chapter IV offers the incorporated paper: "Mobile-Based Oral Chemotherapy Adherence-Enhancing Interventions: Scoping Review". Chapter V presents the paper "Development of a Smartphone Program to Support Adherence to Oral Chemotherapy in People with Cancer", that describes the process of design of the self-management program based on theoretical and methodological frameworks, findings from the formative qualitative study described in Chapter III, and reviews of evidence. Chapter VI presents the paper "A smartphone self-management program to support adherence to oral chemotherapy in people with cancer: proof-of-concept trial", and Chapter VII offers the conclusions, limitations, and recommendations for future research. Figure 2 offers a description of the studies included in this thesis.

Figure 2

Flowchart of the studies in the thesis



1.6. Summary

Medication non-adherence is a global health issue and it is estimated that in developed countries, only half of the chronically ill patients adhere to their treatment. Adherence to OC is key to maximize the effectiveness of the drugs and patients' survival rates, and to reduce the incidence of unwanted health complications such as hospitalizations, relapse, and death. Despite these facts, there is evidence of high rates of OC non-adherence and, due to their developmental stages, AYAs seem to be at a greater risk. Monitoring of adherence to OC and its related side-effects is a key challenge experienced by health professionals and patients due to the lack of standardized surveillance procedures in oncology settings, like those observed in conventional IV therapy. If patients continue to be increasingly responsible for OC self-administration under limited hospital supervision, then it is necessary to provide them with self-management strategies to support their medication adherence.

Due to their extended availability and usability, mobile phones are a promising platform to provide chronically ill patients with support to take their medications as prescribed by their doctor. Although there is a growing body of evidence on the effectiveness of mobile phone SMS-based interventions in increasing treatment adherence in other chronic diseases, the extent to which these interventions are effective in supporting OC adherence is not clear. The purpose of this research was to examine the proof-of-concept of a smartphone self-management program to support adherence to OC in AYA and adults with cancer. A series of studies were conducted to understand the main modifiable reasons for OC non-adherence, to explore the preferences OC users had about the structure of a mobile phone tool to support OC adherence, and to examine what was known about available mobile phone-based OC adherence-enhancing interventions. Findings from the studies described above informed the design of a novel smartphone self-management tool that was tested with AYA and adult OC users. Descriptions of the studies are offered in chapters II-VI of this thesis.

CHAPTER II. Main Modifiable Reasons for Oral Chemotherapy Non-Adherence: Impact, Interventions, and Assessment

2.1. Overview of the Chapter

Knowledge of the underlying reasons for medication non-adherence is essential in the design of OC adherence-enhancing interventions. However, the evidence for factors influencing OC adherence is scarce, especially compared to the body of knowledge in other chronic conditions such as HIV and diabetes. Therefore, it is important to explore evidence for medication adherence in chronic illnesses in a broader context that supports and complements findings related to OC adherence. This chapter aims to determine the main reasons for OC non-adherence that have the potential to be modified by a self-management program intervention delivered via mobile phone. Additionally, this chapter aims to identify key determinants of non-adherence to OC that, although non-modifiable, may be susceptible to be controlled under experimental conditions. To do this, the following information is provided in the next sections: a description of commonly used categorization systems of reasons for medication non-adherence (section 2.2), Paper 1 "A Review of Factors Influencing Non-Adherence to Oral Antineoplastic Drugs" (section 2.3), a comparison between key factors for non-adherence to OC (identified in Paper 1) and medication for chronic diseases (section 2.4), and a review of evidence on the impact of the main modifiable reasons for OC non-adherence, as well as available interventions and methods of assessment of these factors (section 2.5).

2.2. The Multi-Dimensionality of Medication Adherence

The list of determinants of oral medication adherence is vast, with more than 400 factors identified to date (Kardas, Lewek, & Matyjaszczyk, 2013). In an attempt to explain the most relevant factors, authors employ category systems. These systems are based on the concept of adherence as a multi-dimensional phenomenon affected by elements of the therapeutic process (e.g. treatment, patient, healthcare system). One of the most cited

classifications comes from the WHO (Sabaté, 2003), which divides the determinants of medication adherence into five categories: socio-economic factors (e.g. socioeconomic status, social support network, and education), healthcare team and system-related factors (e.g. medication distribution system and duration of consultations), condition-related factors (e.g. comorbidities, symptom severity, and disease progression, and severity), therapy-related factors (e.g. complexity of regimen and side-effects) and patient-related factors (e.g. self-efficacy, knowledge of disease and treatment, and forgetfulness). This classification was developed under the premise that all five dimensions interact to facilitate or reduce medication adherence and that individuals are not solely responsible for their adherence behaviour.

Another popular classification approach focuses on the attribution of responsibility to follow medical prescriptions which can lay with the individual or with factors outside of the individual. According to this classification, non-adherence to oral medication can be explained by two groups of factors: intentional and unintentional (Lehane & McCarthy, 2007). Intentional non-adherence is defined as the human determination to not follow medication prescriptions. This concept considers that patients are actively responsible for adhering (or not) to their medical prescriptions. People may intentionally be non-adherent when altering or stopping medication schedules because they feel better or worse or feel the treatment is not being helpful (Gadkari & McHorney, 2012). On the other hand, the concept of unintentional non-adherence assigns the patient a passive role and cognitive processes are less involved than in intentional non-adherence. Unintentional non-adherence comprises three groups of factors: patient factors (e.g. knowledge and understanding of treatment and forgetfulness), treatment factors (e.g. drug side-effects, duration of therapy and cost), and patient-provider factors (e.g. relationship with health-care professionals and duration of consultation) (Lehane & McCarthy, 2007).

Regardless of the source of factors that influence medication adherence (attributed to

the individuals' intention or spread across the elements of the therapeutic process), evidence on the elevated number of variables and contradiction on their influence on medication adherence makes it impossible to generate a matrix of determinants that allows predicting individual adherence (Kardas et al., 2013). As a consequence, medication adherence is considered a multi-factor phenomenon and it is recommended that adherence-enhancing interventions focus on addressing multiple variables that may impact on medication adherence.

2.3. A Review of Factors Influencing Non-Adherence to Oral Antineoplastic Drugs

2.3.1. Overview of Paper 1.

In this section, a literature review was conducted to provide an up-to-date summary of the main modifiable and non-modifiable reasons for non-adherence to OAD that involve both, OC and oral endocrine therapies. Despite efforts to limit the review to OC drugs, most of the literature reviewed did not differentiate between their findings on these types of drugs and oral endocrine therapies.

Paper 1 is highly relevant to this thesis because the identification of the key modifiable reasons for OC non-adherence (side-effects, forgetfulness, and poor knowledge about OC), together with a review of the evidence on the impact, interventions, and assessment of these factors (described in section 2.4), guided the decisions about the behavioural change strategies incorporated into the development of the smartphone self-management program (Chapter V) tested for proof-of-concept in this research (Chapter VI).

Findings from Paper 1 on both, modifiable and non-modifiable factors for OAD non-adherence, are also useful as a guide to oncology health professionals in their assessment of OAD adherence and may help to inform the development of interventions aiming to improve adherence to OAD.

2.3.2. Paper 1

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REVIEW ARTICLE

A review of factors influencing non-adherence to oral antineoplastic drugs

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Abstract

Purpose Adherence to oral antineoplastic drugs is a complex phenomenon, and knowledge about the reasons that people with cancer do not adhere to their prescriptions is essential to inform adherence-related support in clinical and research contexts. This study aims to provide an up-to-date summary of the key reasons for non-adherence to oral antineoplatic drugs (OAD) in people with cancer.

Methods Electronic databases Medline, Embase, Emcare, and PsychINFO were searched for systematic reviews and studies published between January 2010 and March 2018. Data was analyzed and extracted by two independent reviewers.

Results Three systematic reviews and two studies were included in the review. Key factors for non-adherence were classified as either modifiable or non-modifiable factors. Side effects, forgetfulness, and poor knowledge about OAD were identified as modifiable factors while co-payment, age, regimen complexity. and time since diagnosis were identified as non-modifiable factors. Most of the included studies focused on breast cancer and chronic myeloid leukemia (CML) patients. Low methodological quality and different adherence cut-off rates were observed in the included literature.

Conclusions More research with rigorous methodology and diverse cancer types is needed to increase evidence on the reasons for OAD non-adherence. However, findings from this study may serve to aid in drafting guidelines and suitable interventions for adherence-related support to OAD users.

Keywords Medication adherence · Oral antineoplastic drugs · Cancer · Oncology · Factors

Introduction

Medication adherence is a complex, multifactorial phenomenon affected by treatment, patient, and healthcare system factors. It is defined as the extent to which an individual's medication intake behavior corresponds to that agreed with the health professional [1]. To date, more than 400 determinants of oral medication adherence have been identified [2]. In chronic, non-oncologic diseases, it is estimated that only 50% of patients are adherent to their prescribed medications [1].

Findings reported in this manuscript have not been previously published, and the manuscript is not being simultaneously submitted elsewhere. The authors have full control of all primary data, and they agree to allow the journal to review their data if requested.

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Similarly, in oncology, there is evidence of OAD adherence rates being as low as 46% [3].

OAD include oral chemotherapy, targeted therapies, and hormonal therapies [4]. Of the many advantages in the use of oral versus intravenous antineoplastic drugs, one is the ease of home administration. However, oncology facilities generally do not follow standardized processes to monitor OAD adherence [5] which is a challenge for health professionals and patients. Research-based knowledge of the factors that reduce OAD adherence would be beneficial to oncology practice, allowing accurate individual assessment and the development of interventions and strategies that could translate into improved utilization of OAD and ultimately improved treatment outcomes.

The aim of this review was to provide an up-to-date summary of the main reasons for non-adherence to OAD in people with cancer.

Methods

Search strategy

Two electronic database searches of Medline, Embase, Emcare, and PsychINFO were conducted. Inclusion criteria for the first search were (a) follow a systematic review approach, (b) focus on reasons/determinants/factors for oral chemotherapy/oral endocrine therapy non-adherence, (c) be written in English, and (d) be published between 01/2010 and 03/2018. To identify relevant studies, the following search terms were used: "systematic review, review," "reasons, determinants, factors," "adherence, non-adherence, nonadherence, compliance, noncompliance," "oral chemotherapy/oral endocrine/hormonal therapy/oral antineoplastic drugs," and "cancer, oncology." This resulted in three systematic reviews [3, 6, 7] being included in this study. Due to a gap of almost 3 years between the most recent systematic review and the date of search, a second search was conducted on peer-reviewed, research-based studies, published between June 2015 and March 2018. Inclusion criteria for this search were (a) research-based studies, (b) on reasons for oral chemotherapy/oral hormonal therapy non-adherence, (c) written in English, and (d) published between June 2015 and March 2018. Research design (e.g., qualitative and qualitative) was not an exclusion criterion in the study. However, research protocols were excluded. Two additional studies were added into this review [8, 9].

While a careful search of the electronic databases was conducted, with clear search terms and criteria for inclusion, this study did not intend to be of a systematic nature. This literature review aims to summarize available evidence on the topic, using qualitative methods. The quality of the studies was not an inclusion criteria.

Data analysis

One reviewer, XSR, identified and removed duplicates and assessed the eligibility of the articles by scanning titles and abstracts. Independent assessment of the eligibility of full-text articles was conducted by two reviewers, XSR and KMG. Data from eligible publications were independently extracted by the reviewers and organized according to main categories of reasons for non-adherence to OAD.

Results

The three systematic review articles included in this review focused on patients with diverse cancer types, with a majority of studies on breast cancer. The two research studies focused on oral chemotherapy only in patients with CML [8] and patients with diverse cancer diagnosis including CML [9]. The highest number of studies included in a systematic review was 51 of which only 19 focused on correlates of adherence to oral chemotherapy (non-hormonal), mainly with CML patients. Most of the included studies (3/5) strongly recommended the provision of patient education regarding the use of OAD, as part of standardized procedures that also encompass monitoring of OAD adherence and side effects. The systematic reviews also highlighted the presence of studies with weak methodology and high risk of bias amongst the reviewed literature (e.g., poor specification of target populations and outcomes, small sample sizes, and non-validated subjective measures of adherence). Table 1 summarizes key points from the included articles.

The main reasons for OAD non-adherence identified in the studies were classified according to the World Health Organization framework for factors influencing medication adherence [1] and were divided into modifiable and non-modifiable reasons. For the purposes of this review, modifiable reasons are defined as "those factors of OAD non-adherence that can be modified by the patient or in collaboration with their carers and/or health professionals". A summary of findings is provided in Table 2.

Modifiable reasons for non-adherence to oral antineoplastic drugs

Therapy-related

Side effects and toxicities It is well-recognized that OAD produce several side effects in people with cancer and that the severity of these symptoms may vary according to the type of agent and the individual level of tolerance to the drug. Side effects were identified as the main therapy-related reason for OAD non-adherence in this review [3, 6–9], particularly in breast cancer. In a cross-sectional study with 328 breast cancer

Table 1 Included studies. Reasons for non-adherence to oral antineoplastic drugs

First author/ year/ reference	Purpose of the study	Participants/cancer diagnose/drug type	Study design/data collection	Study limitations	Main findings	Recommendations
Greer [3]	To assess rates and correlates of adherence to oral antineoplastic therapies and interventions aimed at improving adherence	Review period: January 2003–June 2015. Fifty-one individual studies (32 on hormonal therapy and 19 on non-hormonal oral chemotherapy) and 12 papers on intervention studies to improve adherence. Included observational, database, intervention studies, and adults ≥ 18 y/o. Oral chemotherapy and hormonal therapy	Systematic review	Methodological concerns of reviewed intervention studies, limiting generalization of findings. *Predominance of studies on oral hormonal therapy over oral chemotherapy (mainly breast cancer)*. Most of the studies on oral chemotherapy were on CML-targeted drugs	Only few predictors of non-adherence were consistent across studies, making conclusions difficult to draw. Most cited (five or more studies) significant correlates of poor adherence were *Patient factors: younger age/older age, not married/no partner/living alone, high depression, or antidepressant use. *Disease factors: worse survival/higher all-cause mortality and number of co-morbidities showed mixed results across studies. *Treatment factors: greater toxicity/side effects/-symptoms/adverse events. Mixed findings on the influence of the number of medications prescribed on adherence. *Provider and healthcare system factors: greater out-of-pocket costs	*Evidence on strategies to increase adherence to oral chemotherapy is limited. There is a need for new interventions and models of care to address this gap. *Need of further studies using rigorous methodology to address/assess adherence. *Oncology practices should design standard procedures to provide education, reviewing and documenting treatment plans, and monitoring adherence to oral antineoplastic therapy*. Research on new models of care that offer remote monitoring of adherence and side effects are needed
Corrente [6]	To identify causes of non-adherence to oral chemotherapy on the part of the patient and their caregivers	Fifteen articles that fit the following criteria: subjects ≥ 18 y/o, studies using only medications classified as oral anti-neoplastic, qualitative or quantitative, and that examined barriers to adherence to oral chemotherapy. 2010–2015 oral chemotherapy and hormonal therapy	Systematic review	Small sample size with limited number of studies focusing on adherence to oral chemotherapy and presence of studies with poor methodology which may have affected the results of the review. Adherence cut-off rates varied across studies	Main causes of non-adherence are categorized according to adherence dimensions (2 per dimension): *Dimension 1, patient-related: adverse effects/toxicities and forgetfulness. *Dimension 2, system-related: regimen complexity and financial (co-payment) *Dimension 3, nurse/provider related: patient education and frequency and length of follow-up visits	*It is important for nurses to understand the relevance of the provision of oral chemotherapy education to cancer patients and other health staff. *There is limited evidence on barriers to adherence to oral chemotherapy
Verbrugghe [7]	To gain insight into determinants and	Twenty-five articles included. Inclusion criteria:	Systematic review	*Caution required with generalizations due to the	Main reasons of non-adherence to oral anti-cancer therapy:	*Non-adherence to oral anti-cancer therapy is a

Table 1 (continued)

First author/ year/ reference	Purpose of the study	Participants/cancer diagnose/drug type	Study design/data collection	Study limitations	Main findings	Recommendations
	associated factors of non-adherence and non-persistence in patients taking oral anticancer therapy	investigated only oral chemotherapy, assessed factors related to adherence or compliance of oral therapies, subjects > 18 y/o, and research with either a strong or moderate methodological quality. Published between 1990 and April 2012, written in English, French, German, or Dutch. Oral chemotherapy and hormonal therapy		diversity of adherence cut-off rates and measures used in the reviewed studies. *Most literature on breast cancer: (80%) results of this study were primarily relevant to this population	*side effects (the most frequently reported reason), longer duration of treatment, *forgetfulness (the most common reason for unintentional non-compliance) *decreased perceived efficacy of treatment (most common reason for intentional non--compliance), *lack of follow-up appointments and short visit times, *poor patient and family education, *co-payment of ≥ US $30, and *mixed results in how presence of polypharmacy as well as comorbidities affect adherence	multi-factor and complex phenomenon. Patients should be well informed about the long-term benefits of their treatment and how to manage drug-related side effects. This information should be tailored to patients' preferences
Geissler [8]	To assess the extent of suboptimal adherence and investigate motivations and behavioral patterns of adherence in a worldwide patient sample	A total of 2546 participants ≥ 18 y/o, diagnosed with chronic myeloid leukemia (CML) in treatment with oral chemotherapy (tyrosine kinase inhibitors) from 63 countries. Oral chemotherapy (non-hormonal)	Quantitative. Web-based survey (MMAS-8 and questions about reasons and motives for intentional and unintentional non-adherence and interaction with the treating clinician)	Under-representation of participants over 70 y/o	Factors that seemed to be more significant and negatively affect adherence to oral chemotherapy are *younger age (less than 55 y/o), *female gender, *poor management of side effects, *higher dosing frequency, *not feeling well informed about CML by the doctor, *longer time since diagnosis (≥ 1 year), *co-payment: personal co-payment for medication of more than 50 Euros per month	*Patients feeling well informed about their disease exhibited better adherence to OAD. Informing the patients instead of just providing instructions may be more useful. *Every opportunity for improved management of side effects should be taken
Muluneh [9]	To analyze cancer patients' use of oral chemotherapies and to identify opportunities to improve adherence	93 ≥ 18 y/o participants with CML, renal cell carcinoma, breast cancer, and colorectal cancer in treatment with oral chemotherapy.Oral chemotherapy (non-hormonal)	Quantitative. A 30-question survey about frequency and reasons for reducing/skipping doses, sources of information for oral chemotherapy use, perceived importance of food–drug effects, and ease	Use of five different versions of the survey with minor changes that may have influenced the results	*Forgetfulness: 30% of participants. Higher rates of forgetfulness in younger patients (< 50 y/o vs. 50 y/o), shorter treatment duration (<6 months vs. 6 months), or with CML vs. other diagnoses. *Side effects: 35%	*Integrated programs that address barriers to oral chemotherapy adherence should focus on education, on optimal oral chemotherapy use, including food-interactions, and management of

Table 1 (continued)

First author/ year/ reference	Purpose of the study	Participants/cancer diagnose/drug type	Study design/data collection	Study limitations	Main findings	Recommendations
			of understanding labeling directions		(7/20) of intentional non-adherent participants. Thirty-eight percent (8/21) of participants discontinued therapy due to side effects without their doctor's instructions. *Food-drug interactions: 80% ($n = 55$) of the sample did not understand the potential food-drug interactions. *Difficulty understanding label directions was reported by 15% ($n = 14$) of the participants	drug-related toxicities. *There is a gap between oncology practice and evidence which requires multidisciplinary actions to endure optimal oral chemotherapy management with focus on education, validated adherence monitoring tools and management of toxicities

patients, 37/53 participants (69.8%) attributed oral hormonal therapy non-adherence to medication-related side effects [10]. Atkins and Fallowfield [11] also found a significant association ($p = 0.001$) between disliked aspects (e.g., side effects and inconveniences) and non-adherence to OAD medication in breast cancer patients.

In patients diagnosed with CML, findings were mixed. While some evidence pointed towards 50% of patients intentionally modifying OAD doses to avoid side effects (without consulting the treating clinician) [12], there was also evidence of a weak correlation between the number of side effects and adherence to OAD ($p = .032$) [13]. A possible explanation for this disjunction may be that poor management of side effects is likely to have a higher impact on OAD adherence than the mere presence of the side effects in patients with CML. A study with 2546 patients with CML from 63 countries found that the presence of side effects did not have a high effect on adherence but major differences were found between patients who reported their side effects as being well-managed and those who did not think so (40.9% and 24.2% high adherence, respectively, $p = < 0.0001$) [8]. Similarly, Elliason et al. [12] also suggested that finding ways to deal with side effects facilitated adherence to imatinib, an oral small molecule inhibitor, used in the treatment of CML.

Patient-related

Forgetfulness Forgetting to take a dose of OAD was found to be the most cited patient-related reason for non-adherence [6, 7, 9]. In a prospective study of 93 patients treated with OAD for diverse cancers, 30% of participants reported forgetting to take their OAD (non-hormonal) at least sometimes [9]. In a mixed-methods study on the reasons for non-adherence to imatinib in 21 CML patients, 13 (62%) reported instances when they forgot to take their medication [12]. In a study of non-adherence to capecitabine, 23% (10/43) of participants self-reported forgetfulness as the main reason for non-adherence. This included forgetting to pick up medication from the pharmacy, forgetting the verbal instructions provided by the health professional, and forgetting the medication schedule [14].

Having a CML diagnosis (vs. other diagnoses $p = 0.015$), being treated with OAD for more than 6 months ($p = 0.03$), and being younger than 50 y/o($p = 0.002$) were the three factors that were significantly associated with forgetting to take OAD [9].

Poor patient education/knowledge of the disease and treatment

Medication knowledge is the starting point for adherence. This patient-related variable stood out as a modifiable determinant of OAD non-adherence [6, 7]. A study in CML

Table 2 Main reasons for non-adherence to oral antineoplastic drugs

Dimension	Modifiable reasons	Non-modifiable reasons
Socio-economic	N/A	*Cost of drugs (high out-of-pocket cost)* [3, 6–8]
Therapy-related	*Side effects and toxicities* [3, 6–9]	*Regime complexity (higher drug frequency, number of tablets)* [6, 8] *Longer time since diagnose/longer duration of therapy* [7, 8]
Patient-related	*Forgetfulness* [6, 7, 9], *Poor patient education* [6, 7] not being well informed about CML by the doctor [8], food-drug interaction, difficulty understanding label directions [9], *Decreased perceived efficacy of treatment* [7], *Depression* [3]	*Younger age* [3, 7, 8], *Older age* [3, 7]

showed that those who were more satisfied with the information received from their doctor were more likely to adhere to tyrosine kinase inhibitors [8]. In another study, patients' difficulty in understanding drug label instructions and the importance of food-drug interactions led to OAD non-adherence, prompting the authors to recommend these elements to be included as components of future patient education programs [9]. An Australian study conducted with 15 OAD users found that only 46.7% of the participants ($n = 7$) could identify the name of their prescribed OAD, 66.7% ($n = 10$) were familiar with when the medication was due, and 60% ($n = 9$) knew their prescribed dose [15].

Decreased perceived efficacy of treatment [7] and depression [3] were reported as two other modifiable factors for OAD non-adherence, each in one systematic review.

Non-modifiable reasons for non-adherence to oral anti-neoplastic drugs

Socio-economic

Out-of-pocket expenses Greater out-of-pocket costs or co-payments, a socio-economic barrier to OAD adherence, were reported in all of the systematic reviews and one of the research studies [3, 6–8]. Having to pay 30 USD for each drug in diverse cancers [7] and 50 EUR in patients taking tyrosine kinase inhibitors [8] was identified as reasons why patients skipped doses and delayed re-filling OAD prescriptions.

Patient-related

Age Results showed that younger and older patients may be at higher risk of OAD non-adherence [3, 7]. However, there is no consensus on the age cut-off that separates patients at risk from patients who may be more adherent. For example, Verbrugghe et al. [7] found that being less than 45 y/o and older than 85 y/o were risk factors for OAD non-adherence. However, in patients with CML, the risk of non-adherence to OAD prescriptions was higher in individuals younger than 55 years old, and the effect on adherence in older patients was not reported. This may be due to the underrepresentation of patients over 70 y/o in this study [8]. It may be possible that differences in ages at risk of OAD non-adherence can be attributed to differences in cancer and OAD types.

Therapy-related

Regimen complexity Complex drug schedules which involve multiple dosing frequencies, number of tablets, and treatment cycles were found to be reasons for OAD non-adherence in two studies [6, 8]. A pilot study found high OAD adherence rates in patients who received continuous treatment (88%) versus those prescribed OAD in a cycle of 14 days on and 7 days off (35%) and in 7 days on and 7 days off cycle (33%) [16]. There was also evidence that once a day dosing of OAD increased adherence in CML patients compared with multiple doses per day [8].

Time since diagnosis/duration of therapy This factor was identified by two studies [7, 8]. Lower rates of OAD adherence were found in CML patients who were more than 2 years post-diagnosis [8]. Long durations of therapy with OAD were also found to have a negative impact on adherence in patients with breast cancer, CML and others, such as gastrointestinal and brain cancers [7]. More than 6 months of treatment with OAD was related to forgetting to take the drugs [9].

Discussion

This review was conducted to identify modifiable and non-modifiable factors associated with non-adherence to OAD. Caution should be taken when generalizing findings from this review due to a higher prevalence of research on adherence to OAD with CML and breast cancer patients, variations in adherence cut-off rates, and assessment methods across the

studies. Additionally, the reasons for non-adherence to hormonal and non-hormonal oral chemotherapy were not analyzed separately by the systematic reviews. There is a possibility that specific factors influence non-adherence behaviors for each type of OAD, considering evidence of higher rates of non-adherence to non-hormonal compared with hormonal therapies [3].

OAD adherence is a multifactorial and complex phenomenon and, to date, prediction of individual causes of OAD non-adherence has not been possible [2]. Evidence for OAD non-adherence is limited compared with that in chronic illnesses. A number of key modifiable and non-modifiable factors stood out in this review, which have also been identified to affect medication adherence in general chronic diseases.

Key modifiable reasons for OAD non-adherence were side effects, forgetfulness, and lack of OAD knowledge. Side effects were the most common reason for non-adherence. These findings are in concordance with evidence in other chronic diseases, whereby drug-related symptoms were one of the main reasons for the interruption or modification of prescribed medication doses [2, 17]. Even though this review showed poor management of side effects leading to OAD non-adherence in CML patients, there is a lack of evidence for this in other cancer types. Future studies should investigate whether the inability to manage side effects plays a role in OAD non-adherence in other cancer diagnoses.

Findings on forgetfulness as the main patient-related reasons for OAD non-adherence are also consistent with evidence in other chronic diseases [2, 17, 18]. Additionally, a number of factors such as having a CML diagnosis, treatment duration of more than 6 months, and being younger than 50 y/o, seem to increase the risks of forgetting to take OAD [9]. Findings on higher risk of forgetfulness in patients younger than 50 y/o are interesting, considering that cognitive decline is likely to lead to forgetfulness in older patients.

Poor OAD knowledge was the third modifiable reason for OAD non-adherence. A worldwide lack of standardized monitoring procedures for OAD adherence has been previously highlighted [19], and in South Australia, anecdotal data points to a lack of OAD education in hospitals. Although clinicians are the first information providers, in many cases, it is unclear if more extensive or follow-up education should be provided by oncology nurses or pharmacists. Evidence in other chronic conditions shows that the lack of understanding of treatment negatively impacts on medication adherence [2], and chronically-ill patients have expressed their desire to receive more education from healthcare professionals [20]. This is highly relevant as cancer patients remember very little of the information they receive on their first OAD education session [21]. This emphasizes the need for OAD and other treatment-related information to be frequently reinforced in subsequent education sessions.

The main non-modifiable factor identified for OAD non-adherence was co-payment. It affects both treatment implementation and initiation. This has also been identified as a barrier to medication adherence in other chronic conditions [17].

Even though age was identified as a factor in OAD non-adherence, there was no agreement on the definition of "younger" and "older" across the studies. Being "younger" was identified as a barrier for medication adherence in chronic diseases, such as pulmonary hypertension [22] and hepatitis B [23], but this was not consistently observed in other chronic illnesses [2].

More rigorous research including randomized controlled trials with bigger samples, a combination of subjective and objective adherence assessment methods, and other cancer and OAD types (especially non-hormonal oral chemotherapy drugs), is needed in order to broaden the understanding of key barriers to OAD adherence. Additionally, more information is necessary about whether hormonal and non-hormonal agents pose different barriers to OAD adherence. Future literature reviews may also help to broaden this knowledge. This review is designed to be used as a guide for oncology health professionals and researchers in addressing modifiable factors for OAD non-adherence, such as side-effect management, forgetfulness, and knowledge about OAD. It is also important for health professionals to be aware of those non-modifiable factors.

Conclusions

Medication adherence is a multifactorial phenomenon, and this review found a number of factors that explain non-adherence to OAD. While more research with rigorous methodology and diverse cancer types is needed to increase understanding about the factors that influence non-adherence to OAD, this study may serve as a guide to oncology health professionals in their adherence-related conversations with OAD users and in their referral to appropriate medication adherence support measures, such as information resources, reminders, and where available, internet, and/or mobile-based adherence interventions.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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2.4. Comparison between the Key Factors for Non-Adherence to Oral Chemotherapy and Medication for Chronic Diseases

In the overview of Paper 1, it was highlighted that the lack of evidence with an exclusive focus on OC non-adherence did not make it possible to isolate key factors for non-adherence from those relevant to oral endocrine therapy. There is a strong body of evidence on the reasons that chronically ill people fail to take their medications as prescribed. A review of this evidence was conducted to explore similarities between the key factors for non-adherence to medication for chronic diseases and OAD. As outlined below, the presence of these similarities suggest that the challenges associated with medication adherence are common between OAD (which include both, OC and oral endocrine therapies) and medication for chronic conditions.

A literature review was conducted to find the most recent systematic review of the reasons for medication non-adherence in chronic diseases. A comprehensive exploration of published systematic reviews was conducted in the databases Medline, EMBASE, EMcare, and PsychINFO. To meet the search criteria, articles needed to: follow a systematic review approach, be focused on the reasons/factors/determinants for medication non-adherence in chronic diseases, and be written in English. The most recent result meeting the search criteria (Kardas et al., 2013) left a knowledge gap of five years to the date of this review (March 2018). For this reason, a qualitative meta summary and triangulation with quantitative evidence study was also included (Irwin & Johnson, 2015). According to search results, no systematic or literature reviews were published after 2015.

A second search was conducted to uncover evidence from 2015 to March 2018. This search included research-based studies, focused on reasons for non-adherence to medication for chronic diseases, and written in English. Four additional studies were incorporated into this review (Allard et al., 2017; Grady, Weiss, Hernandez-Sanchez, & Pepke-Zaba, 2018; Guénette et al., 2015; Pagès-Puigdemont et al., 2016).

Data extracted from the included articles were analysed to identify the main factors for medication non-adherence. The relevance of each factor was determined based on the number of studies supporting its influence on medication non-adherence.

The availability of literature on determinants of medication non-adherence in chronic conditions is extensive compared to that in OAD non-adherence. In chronic diseases, a total of 51 literature reviews were explored by Kardas et al.'s systematic review (Kardas et al., 2013) and 159 studies were reviewed by Irwin and Johnson's literature meta summary (Irwin & Johnson, 2015), with four additional research-based studies available after the previous reviews took place. In the case of OAD adherence, the most recent systematic review (Greer et al., 2016) included 51 individual studies, of which only 19 of them were conducted in OC users. Two additional research-based studies were identified after the systematic review took place.

A possible explanation for the difference in the amount of evidence between medication used in chronic diseases and OAD is that the increase in the availability and widespread use of OC agents is from recent data (last two decades) due to the development of targeted therapies which are now used as first line of treatment for some cancer types (e.g. CML). Additionally, evidence on chronic diseases includes studies conducted in many illnesses, compared to only OAD in cancer.

In chronic diseases, eight key modifiable and four non-modifiable factors for medication non-adherence were identified. In the case of OAD non-adherence, five modifiable and five non-modifiable key factors were identified in Paper 1. Table 3 shows the main reasons for non-adherence to OAD (from Paper 1) and medication for chronic diseases. These findings are consistent with the consensus on medication adherence as a multi-factorial and complex phenomenon with no single determinant responsible for predicting the degree of individual adherence.

The studies on the reasons for non-adherence to OAD and medication for chronic

diseases were conducted in adults ≥ 18 y/o, with the exemption of a review of systematic reviews that included all age groups (children and adults) (Kardas et al., 2013). This means that evidence on the reasons that adolescents fail to adhere to their prescribed medications and OAD was lacking in this review. Additionally, the design of the reviewed studies did not allow determination of the factors affecting non-adherence to medication for chronic diseases and OAD in young adults (18-25 y/o), compared to adults (> 25 y/o).

TABLE 3

Modifiable and non-modifiable reasons for non-adherence to medication for chronic diseases and oral antineoplastic drugs from (Skrabal Ross, Gunn, Suppiah, Patterson, & Olver, 2020)

	Modifiable reasons for non-adherence		**Non-modifiable reasons for non-adherence**	
Factors	Chronic diseases	Oral antineoplastic drugs	Chronic diseases	Oral antineoplastic drugs
Socio-economic	Lack of family and social support (Kardas et al., 2013; Pagès-Puigdemont et al., 2016)	N/A	Cost of drugs (high out-of-pocket cost) (Irwin & Johnson, 2015; Kardas et al., 2013)	Cost of drugs (high out-of-pocket cost) (Corrente 2016; Geissler et al., 2017; Greer et al., 2016; Verbrugghe et al., 2013)
Healthcare Team and System-Related	Poor patient–physician communication (Kardas et al., 2013; Pagès-Puigdemont et al., 2016)	N/A	N/A	N/A
Condition-Related	N/A	N/A	N/A	N/A
Therapy-Related	Adverse effects (Irwin & Johnson, 2015; Kardas et al., 2013)	Adverse effects and toxicities (Corrente 2016; Geissler et al., 2017; Greer et al., 2016; Muluneh et al., 2018; Weingart et al., 2008)	Regime complexity (pill burden) (e.g., complex/frequent dosing schedule/number of tablets) (Grady et al., 2018; Irwin & Johnson, 2015; Kardas et al., 2013; Pagès-Puigdemont et al., 2016) Longer duration of treatment (Grady et al., 2018; Kardas et al., 2013)	Regime complexity (higher drug frequency, number of tablets) (Corrente 2016; Geissler et al., 2017) Longer time since diagnose (Geissler et al., 2017; Verbrugghe et al., 2013)
Patient-Related Factors	Forgetting (Guénette et al., 2015; Irwin &	Forgetfulness (Corrente 2016; Muluneh et al., 2018;	Younger age (Allard et al., 2017; Grady et al.,	Younger age (Geissler et al., 2017; Greer et

Johnson, 2015; Kardas et al., 2013)	Verbrugghe et al., 2013)	2018; Kardas et al., 2013)	al., 2016; Verbrugghe et al., 2013)
Lack of comprehension of the disease and treatment, side effects (Kardas et al., 2013; Pagès-Puigdemont et al., 2016)	Poor patient education (Corrente 2016; Verbrugghe et al., 2013), not being well informed about CML by the doctor (Geissler et al., 2017) food-drug interaction, difficulty understanding label directions (Muluneh et al., 2018)		Older age (Greer et al., 2016; Verbrugghe et al., 2013)
Negative patients' beliefs about the efficacy of treatment (Kardas et al., 2013; Pagès-Puigdemont et al., 2016)	Decreased perceived efficacy of treatment (Verbrugghe et al., 2013)		
Psychiatric illness, e.g. anxiety/depression (Kardas et al., 2013) depression mainly in cancer patients (Irwin & Johnson, 2015)	Depression (Greer et al., 2016)		
Being away from home (Guénette et al., 2015; Kardas et al., 2013)			

2.4.1. Modifiable reasons for non-adherence to medication for chronic diseases and oral antineoplastic drugs.

As described in Paper 1, drug-related side-effects/adverse effects/toxicities is the main therapy-related reason for non-adherence to OAD. In people treated with OAD, side-effects are known to be related to temporary drug cessation, dose omissions, and discontinuation without notifying the oncologist (Corrente 2016; Geissler et al., 2017; Greer et al., 2016; Verbrugghe et al., 2013). This is supported by findings from studies in chronic diseases that highlight the negative effect of adverse effects on medication adherence as reported by studies with patients diagnosed with HIV, osteoporosis, mental illness (depression, psychosis), and tuberculosis (Irwin & Johnson, 2015; Kardas et al., 2013).

Forgetfulness is a key patient-related factor related to non-adherence to medication for

chronic diseases and OAD. In literature review studies on chronic diseases, most of the studies supporting forgetfulness as a reason for non-adherence were conducted in patients diagnosed with HIV, hypertension (Irwin & Johnson, 2015; Kardas et al., 2013), and type-2 diabetes (Guénette et al., 2015).

Another main patient-related factor for medication non-adherence common to both, chronically ill patients and people treated with OAD, is poor knowledge about treatment. In chronic diseases a statistically significant correlation between oral medication knowledge and self-reported rates of adherence to oral medication was reported in a sample of 765 patients ($r = 0.964$, $p < 0.001$) (Okuyan, Sancar, & Izzettin, 2013). In patients with hypertension, a statistically significant correlation was also found between a high level of hypertension management knowledge (assessed by the Hypertension Knowledge-Level Scale HK-LS) and higher scores in medication adherence (assessed thought MMAS-8) ($p= 0.038$) (Jankowska-Polańska, Uchmanowicz, Dudek, & Mazur, 2016). Both, chronically-ill patients and people treated with OAD have expressed their need to receive more education and information from healthcare professionals (Pagès-Puigdemont et al., 2016; Simchowitz et al., 2010).

Two modifiable reasons for OAD non-adherence were identified in Paper 1 but the number of studies supporting this evidence was not as high as in other factors: depression and negative perceptions about the efficacy of treatment. The presence of psychiatric illness (e.g. anxiety/depression) showed a negative effect on medication adherence in chronically ill patients (Kardas et al., 2013) but seemed to especially affect cancer patients when compared to those with other chronic diseases (Irwin & Johnson, 2015). Negative beliefs or perceptions about the efficacy of treatment is also a common modifiable reason that people treated with medication for chronic diseases have poor medication adherence.

This review of evidence in chronic diseases identified a number of key factors for medication non-adherence which did not seem highly relevant or studied in the case of OAD. These are the lack of family and social support (socio-economic factor), poor patient-

physician communication (healthcare team and system-related factor) and being away from home (patient factor). Key modifiable reasons related to the "condition" were not identified in chronic diseases or OAD studies and no socio-economic or healthcare and system-related factors were highlighted as key modifiable reasons for non-adherence to OAD in Paper 1. In the context of this review, this means that those factors have not been highlighted by many studies, possibly because there is a need for more evidence or the available studies have focused on other categories of factors.

2.4.2. Non-modifiable reasons for non-adherence to medication for chronic diseases and oral antineoplastic drugs.

The high out-of-pocket cost of medication stood out as the main socio-economic factor for medication non-adherence in chronically ill patients and those treated with OAD. In many countries, health systems partially cover the cost of medications used to treat chronic diseases and cancer. The remaining gap is to be paid by patients and in some cases, they may not be able to afford the high gap-related costs. For example, in one of the studies reviewed by Irwin and Johnson (Irwin & Johnson, 2015), patients who were non-adherent to heart medication after myocardial infarction reported that the cost of the drugs was one of the reasons for discontinuance of their treatment. Although patients with financial needs in the United States can access social programs and pharmaceutical assistance, the waiting time for this support leads to delays in medication refills, which harms the control of the disease (Garavalia, Garavalia, Spertus, & Decker, 2009).

In a number of less developed countries, patients with HIV may exhibit non-adherence to antiretroviral drugs due to the high out-of-pocket cost of the drugs. Examples of this are India (Joglekar et al., 2011; Kumarasamy et al., 2005), Thailand (Ruanjahn, Roberts, & Monterosso, 2010), South Africa (Aspeling & Van Wyk, 2008) and Egypt (Badahdah & Pedersen, 2011). In the case of OAD, having to pay US $30 for each drug in diverse cancers (Verbrugghe et al., 2013) and 50 Euros in patients taking tyrosine kinase inhibitor drugs

(Geissler et al., 2017) was identified in Paper 1 as a reason that patients skip doses and delay refilling OAD prescription.

The complexity of the regimen and longer time since diagnosis or treatment were the main therapy-related factors for medication non-adherence in chronic diseases and cancer treated with OAD. Pill burden or taking a large number of pills for different medical conditions was found to negatively affect medication adherence in chronic diseases in almost all of the reviewed studies (Grady et al., 2018; Irwin & Johnson, 2015; Kardas et al., 2013; Pagès-Puigdemont et al., 2016). However, there is also conflicting evidence that taking a large number of pills may be linked to good medication adherence as reported by six of the reviewed studies in Irwin and Johnson's literature review and meta summary (Irwin & Johnson, 2015). These findings may indicate that individuals who need to take many pills daily develop effective routine adherence systems to succeed in following their medical plans. In people treated with OAD, people prescribed continuous cycle treatment (Spoelstra et al., 2013) and those who take one OAD dose daily versus multiple doses (Geissler et al., 2017) seem to show higher adherence to OAD.

In chronic diseases such as tuberculosis, HIV, hypertension (Kardas et al., 2013), and pulmonary hypertension (Grady et al., 2018), longer duration of treatment has been shown to negatively affect medication adherence. In OAD therapies, longer time since diagnosis is a key therapy-related factor for non-adherence.

Age has been highlighted as an important patient-related factor for medication non-adherence. However, this evidence is conflicting in chronic diseases. Although a number of studies found higher rates of medication non-adherence in younger patients diagnosed with hepatitis B (Allard et al., 2017), pulmonary hypertension (Grady et al., 2018) and diverse chronic diseases (Kardas et al., 2013), several studies have also produced evidence that age does not affect medication adherence (Kardas et al., 2013). As reported in Paper 1, being younger and older has been related to OAD non-adherence. However, there were no clear

definitions for these age ranges.

None of the non-modifiable key reasons in this review were related to the category "condition". In the case of OAD, no key reasons for non-adherence were identified in the category "healthcare and system- related factors".

This review shows that people treated with OAD and medication for other chronic diseases share common barriers to medication adherence. This suggests that evidence on the main reasons for OAD non-adherence is likely to be applicable to both OC and oral endocrine therapies. There is an opportunity for future studies investigating adherence to OAD to study the impact of socio-economic, healthcare and system, and condition related factors on non-adherence to OAD.

2.5. Main Modifiable Reasons for Oral Chemotherapy Non-Adherence. Evidence on Impact, Interventions, and Assessment Tools

The main modifiable reasons for OC non-adherence were identified and described in Paper 1 (section 2.2). Evidence on the relationship between each of these variables and OC non-adherence as well as a description of assessment tools and interventions designed to positively modify these factors are offered in the following sections.

2.5.1. Drug-related side-effects/symptoms. Impact on adherence to oral chemotherapy, interventions, and assessment.

Patients' reports show that symptoms are temporal. They are experienced for a limited time (minutes to days) with periods of symptom absence (Kroenke, 2001). The side-effects from OC are similar to IV therapy. Some of the most common OC-related symptoms are fatigue, pain, numbness and tingling, sleep disturbance, diarrhoea, distress, swelling of hands and feet, lack of appetite, shortness of breath, redness, swelling and pain in hands and feet, constipation, skin rash, nausea/vomiting, mouth sores, fluid retention, dizziness, chemo brain, and weakness (Spoelstra, Given, Sikorskii, Majumder, et al., 2015).

OC-related side-effects may decrease patients' quality of life, leading to a dose being

modified or missed by the patient, in many cases without prior consultation with a clinician (Timmers et al., 2016). In a survey with 93 cancer patients prescribed OC to treat CML, renal carcinoma, breast cancer, and colorectal cancer, 38% (8/20) of the participants who reported cutting back on their medication, discontinued OC therapy due to adverse effects without notifying their physician (Muluneh et al., 2018). An observational study reported that side-effects was the main reason for a third of 92 patients diagnosed with diverse cancer types to discontinue treatment with capecitabine (Timmers et al., 2016). Previous research with CML patients established the possibility that poor management of side-effects had a higher impact on OC non-adherence than the presence or severity of symptoms (Eliasson, Clifford, Barber, & Marin, 2011; Noens et al., 2009). This was also found in patients with gastrointestinal cancers. A recent study with patients treated with capecitabine showed no significant correlation between the mean severity of side-effects and adherence to the drug (with the exemption of the symptom diarrhoea). However, participants who self-evaluated their self-management of side-effects as effective were more likely to be classified as adherent versus those who were non-adherent to capecitabine at week 1 ($p= 0.04$). Even though it was not significant, there was a trend between self-management of side-effects and adherence at weeks 2 and 4 ($p= 0.06$ and $p= 0.05$ respectively) (Jiang et al., 2019).

There is also evidence that OC-related adverse effects affect medication adherence in AYA. In a survey with 17 young cancer patients (18-39 y/o), 59% reported that side-effects were a barrier to OC adherence (Divakaruni, Saylor, & Duffy, 2018). The definition of AYA ages in the study differs from that in the present research (15-25 y/o) and it is important to highlight that more than half of the sample were older than 25 y/o.

Two nurse-led interventions (not focused on OC adherence) demonstrated an effect in improving some chemotherapy-related side-effects. These interventions involved the assessment and delivery of evidence-based, self-management advice and information about side-effects. Both studies showed significant improvement in nausea, vomiting, and oral

problems compared to pre-test data (Kearney et al., 2008) and fatigue (p= 0.040) compared to the control group (Kearney et al., 2009). However, no improvement was seen in other symptoms targeted by the interventions. Although most of the patients in both studies were treated with traditional chemotherapy agents, one of the studies included OC drugs (e.g. capecitabine) (Kearney et al., 2009). Both studies used the Chemotherapy Symptom Assessment Scale (Brown et al., 2001) to assess incidence, severity, and associated distress of chemotherapy symptoms. This tool had been used in previous studies and has been tested for criterion and construct validity, reliability and internal consistency (α= 0.75). Kearney et al.'s study (2009) also used the National Cancer Institute's Common Toxicity Criteria Adverse Events (CTCAE) grading system (The National Cancer Institute, 2017) to assess the severity of side-effects. This intervention was delivered via a mobile phone app with a real-time report of side-effects sent to the research team.

Side-effect-related assessment, information, and management strategies have also been found to be effective in improving adherence to OC. An example of this is an observational, two-cohort study (C1 n= 50, C2 n= 100) with adults diagnosed with advanced non-small cell lung cancer and treated with erlotinib (Gebbia et al., 2013). The intervention consisted of an adherence monitoring program in which patients and their caregivers were provided with verbal and written information on treatments' expected side-effects. Participants were asked to report unexpected or severe side-effects to the research team. Patients who took part in the monitoring program (C2) showed significantly better adherence to treatment than patients who were not included in the program (C1) (adherence by pill counting was 78% in C1 and 87% in C2, p= 0.002). Study findings showed a significant correlation between the number of adverse events and patient-reported adherence, with higher numbers of side-effects being correlated to higher rates of non-adherence to erlotinob (p= 0.0001). Symptom presence and severity was measured by the CTCAE grading system. The most commonly reported adverse effects were skin rash (76%), diarrhoea (42%), and fatigue

(64%). Findings from this study suggest that verbal and written provision of information about expected erlotinib's side-effects and their timely reporting to the treating team may lead to a significant increase in drug adherence.

Education of side-effect management has also been used in combination with cognitive-behavioural strategies to reduce the incidence and severity of chemotherapy-related side-effects. These interventions focus on one symptom or a particular cancer site (Sherwood et al., 2005). Cognitive-behavioural interventions that use problem-solving operate under the premise that when instructed to include symptom management behaviours into their repertoire, patients will effectively manage their symptoms by adopting of a positive orientation towards symptoms, identifying attainable goals, implementing and verifying the effectiveness of the strategies to manage their symptoms (D'Zurilla & Nezu, 2001). An example of the use of combined problem-solving strategies and education is a RCT with 124 adults diagnosed with advanced-stage cancer. Nurses with experience in oncology delivered an intervention over eight weeks to teach patients problem-solving techniques to address symptom severity. The intervention was designed to support patients in understanding the nature of the symptoms, improve patients' belief in symptom-control and instruct patients on problem-solving skills. Symptoms assessed during each contact were pain, fatigue, nausea, vomiting, insomnia, dyspnoea, weakness, anorexia, fever, dry mouth, constipation, mouth sores, and depressive symptoms. Symptom severity was measured by asking patients to rate the severity of each symptom using a scale from 0 (not present) to 10 (worst severity) and then adding severity ratings for each symptom. Patients in the experimental group (EG) reported a significant reduction in the mean symptom severity at 10 weeks compared to the control group (CG) (EG 19.1, SD = 13.1, CG 27.7, SD = 18.9) (Sherwood et al., 2005).

Two longitudinal, single-arm with comparison group studies of pharmacy-led, multi-strategy interventions found an increase in adherence to OC in patients with CML and renal cell carcinoma. The interventions included information about OC side-effects and their

management. The first study had a sample of 269 CML patients treated with tyrosine kinase inhibitors, with average participation of 31.9 months. The adherence-enhancing strategies included education about drug and disease, adherence monitoring, symptom management, and reminders for medication refills. Post-intervention adherence (assessed through prescription and medical records) was significantly higher in the intervention group versus the control group (88.6% vs 65.8%) ($p= 0.004$) (Lam & Cheung, 2016). The second of these studies was conducted with 50 Japanese renal cell carcinoma patients prescribed pazopanib. In this intervention, pharmacists monitored participants in person or over the phone to address side-effects and to provide supportive care. The intervention group showed significantly better adherence (100%) than the control group (data from 13 patients collected prior to intervention) (62%) at post-intervention ($p< 0.001$). Adherence was assessed through a self-report diary. Nausea and anorexia were significantly lower in the intervention versus control group (nausea 3% and 38% respectively, $p= 0.003$; anorexia 8% and 46% respectively, $p= 0.005$) (Todo et al., 2019).

The previously described pharmacy-led OC adherence-enhancing interventions involved a number of contacts with patients over time, were tailored to patients, and delivered OC-related symptom information and management advice. Although the structure and content of the symptom management strategies were not provided in the reviewed articles, the interventions were delivered by trained pharmacists (face-to-face or over the phone). Evidence shows that pharmacy-led programs are highly accepted by patients, leading to improved OC adherence, clinical and economic outcomes (Muluneh et al., 2018; Wong, Bounthavong, Nguyen, Bechtoldt, & Hernandez, 2014). It was not possible to identify the assessment tools used to measure the presence and severity of side-effects in the two pharmacy-led studies.

Unlike the above-mentioned pharmacy-led intervention, RCTs of multi-strategy interventions by non-pharmacists have shown no significant effects in increasing OC

adherence and improving side-effects. The effect of three interventions combining cognitive-behavioural therapy and educational/information strategies to reduce OC-related side-effects and to increase adherence was evaluated in a sample of 119 adults diagnosed with solid tumours and treated with OC (Spoelstra et al., 2013). Participants were randomised to one of three interventions: automated voice response system to assess symptoms and adherence (AVR) alone (n=40), AVR with strategies to manage symptoms and adherence (n=40), and AVR to manage adherence (n=39). All of the groups received a hard copy of the Symptom Management Toolkit (Given et al., 2008). This kit had a notebook format, compiled frequently asked questions, was written using patient-friendly language and provided information on what was needed to manage cancer and treatment-related symptoms. The Symptom Management Toolkit has been successfully used in previous studies (Spoelstra et al., 2013 ; Spoelstra, Given, Sikorskii, Coursaris, et al., 2015). Patients who reported high-severity symptoms in group one were referred to the Symptom Management Toolkit for self-management of symptoms, those in group two (high-severity symptoms or low adherence report) received a nurse call to deliver symptom management and/or adherence strategies. Participants in group three who reported low adherence received a nurse call to deliver adherence-enhancing strategies. Nurses' calls continued weekly until patients reported low symptom severity or adherence reached 100%. Symptom presence and severity were measured using the Symptom Experience Inventory (Given et al., 2008) with consistency reliability of α=0.79. The inventory gathered information about the presence of symptoms in the last seven days (yes or no) and the severity of symptoms rated on a scale from 0 to 10 (not present to worst imaginable). The inventory included 15 common chemotherapy-related side-effects: fatigue, pain, insomnia, poor appetite, constipation, nausea/vomiting, anxiety, cough, depression, diarrhoea, mouth sores, shortness of breath, peripheral neuropathy, difficulty remembering, and weakness. A decline in symptom severity over time was observed in all three groups and no differences in adherence were found between the AVR system alone and

the AVR system plus nurse calls to deliver symptom management strategies (G1 mean baseline 16.9 SD 11.8, mean exit 11.0 SD 10.4, G2 mean baseline 18.5 SD 16.1, mean exit 11.6 SD 12.1; G3 mean baseline 26.0 SD 16.7, mean exit 20.1 SD 16.0).

Another intervention included a combination of SMS medication reminders and written information on how to manage side-effects (Sikorskii et al., 2018; Spoelstra, Given, Sikorskii, Coursaris, et al., 2015). In this 12-week RCT with 80 cancer patients treated with OC, the experimental group (n=40) received daily SMS medication reminders (content based on social cognitive theory) on their mobile phones and a response yes/no response based on medication intake (or not) was expected. Additionally, a hard copy of the Symptom Management Toolkit was provided to the experimental group at the beginning of the study. Adherence was measured through the ratio of dose intake or pill counts and symptoms were assessed weekly using the Symptom Experience Inventory. The questionnaire assessed the presence and severity of 18 main OC-related side effects (pain, fatigue, sleep disturbance, anxiety, weakness, headaches, skin rash, numbness or tingling, redness or peeling in hands or feet, swelling, joint pain, mouth sores, lack of appetite, nausea or vomiting, diarrhoea, constipation, cough, and shortness of breath) and symptom severity was rated between 1(low severity) and 9 (high severity). This study did not find statistically significant differences in adherence and symptoms between the experimental and control group. The authors stated that participants' adherence rates to OC were already high at baseline, making it difficult to be increased by the intervention. Symptom severity was significantly lower ($p< 0.01$) in the experimental arm at week eight, but not at weeks four or 12, compared to the control group. The authors also reported differences in adherence scores between the two assessment tools employed (self-report and relative dose intensity, or the ratio of pharmacy-delivered OC doses over a period concerning what was prescribed by the doctor). The relative dose intensity method could not be used to assess adherence in all participants because of the unavailability of medical records to confirm OC dose changes, and groups' overall adherence scores were

higher through this method.

Information about the management of OAD side-effects was highlighted as an important feature in a mobile phone app to enhance adherence to OAD. A recent cross-sectional study with 409 potential users of a mobile phone app-based intervention showed a preference for strategies to manage side-effects (60.2%), information about OAD (65%) and information about the disease (60.2%). Study participants were mainly female (71.1%), Chinese (81.2%), married (72.4%), and treated for breast cancer (51.6%) (Ali, Leow, Chew, & Yap, 2018).

In AYA, a recent mixed methods study found an iPad-based symptom assessment tool to significantly improve self-efficacy for managing symptoms related to chemotherapy (not OC exclusively) over time in all 88 AYA (15-29 y/o) participants ($p= 0.034$). The computerized tool was designed to create a graphic image of participants' symptoms. Participants reported symptoms daily and identified relationship between symptoms and groups of symptoms (clusters), named them, and selected those with higher priority for management (Erickson et al., 2019).

2.5.2. Forgetfulness. Impact on oral chemotherapy adherence, interventions and assessment.

Remembering to take a medication involves a variety of cognitive executive functions required for the control of behaviour, for example attentional control, working memory and everyday cognition, or the ability to solve daily cognitive-complex problems (e.g. medication use, food preparation). Besides the functions involved, being busy also affects individuals' ability to remember to take a medication, with notorious differences between young (18-20 y/o) and old (60-89 y/o) patients. Previous research has shown that young people remember to take medications on days when they are very busy while older people are more likely to remember to take their medications on those days when they are not very busy (Neupert, Patterson, Davis, & Allaire, 2011).

Forgetting to take OC doses is the most common unintentional reason for not following oral medication prescriptions in cancer patients (Verbrugghe et al., 2013). Self-reports of forgetfulness as the main reason for missing OC doses has been reported by studies with CML (Eliasson et al., 2011; Muluneh et al., 2018), breast, and colorectal cancers (Bhattacharya et al., 2012). In a cohort of patients with diverse cancer types, three factors were found to significantly increase the risk of failing to remember to take OC: having a CML diagnosis, being treated with OC for more than six months and being younger than 50 years old (Muluneh et al., 2018).

In AYA, one study found that 47% of a sample of 17 OC users (18-39 y/o) reported forgetfulness as a barrier to OC adherence (Divakaruni et al., 2018).

Data on participants' forgetfulness in OC adherence studies is commonly derived from their answers to one or two questions in surveys or interviews that were designed with the wider purpose of measuring medication adherence. Examples of validated medication adherence tools that have been used in the assessment of forgetting to take OC doses are the MARS-5 which contains one item assessing forgetfulness "I forget to take it" (Bhattacharya et al., 2012), and the MMAS-8 which has one item assessing forgetfulness: "Do you ever forget to take your medication?" (Larizza, Dooley, Stewart, & Kong, 2006). Modified versions of validated adherence self-report questionnaires have also been used in assessing OC-related forgetfulness (Muluneh et al., 2018). Semi-structured interviews which include one question related to forgetfulness (e.g. how often do you forget to take your tablets?) have also been used to assess the variable amongst non-adherent OC users (Eliasson et al., 2011) and similar to that case of self-report questionnaires, the interviews were the same tool used to measure medication adherence (Atkins & Fallowfield, 2006).

A number of reminder strategies have been employed to address the issue of forgetfulness, including alarms, pillboxes, calendars, and drug reminder charts (Hall et al., 2015). More recently, advances in technology have allowed new platforms to deliver

medication reminder strategies. For example, MEMS allows visualization of the number of medication doses taken and programs an alarm at the time of due medication intake or sends SMS reminders to the patient when a dose was not taken on time.

In chronic illnesses in general, mobile phones are being increasingly used to deliver medication adherence self-management strategies with SMS and mobile apps being the most commonly employed platforms (Hamine et al., 2015). The use of electronic medication reminders (especially SMS) has been found to significantly improve medication adherence in chronically ill patients in the short term (Vervloet et al., 2012).

A scoping review of mobile phone-based interventions specifically aiming to enhance OC adherence, described in Chapter IV of this thesis, identified four interventions all of which included medication reminder strategies (Skrabal Ross, Gunn, Patterson, & Olver, 2018). These interventions were found to be helpful for participants to remember to take their OC. Reminder components of the interventions consisted of daily SMS reminders (Pereira-Salgado et al., 2017; Spoelstra et al., 2016) and mobile phone app daily reminder alarms (Brett, Watson, Boulton, & Stoner, 2018; Fishbein et al., 2017). In a more recent study, a mobile game designed for breast cancer patients aiming to improve OC adherence included, amongst other strategies, quests for taking medication and reminder alarms. Statistically significant higher OC adherence in the game group versus the control group was found ($p < 0.001$) and 61% (22/36) of the participants reported that the game helped their medication adherence (Kim, Shin, Jang, Kim, & Han, 2018).

A recent 12-week, single-group study conducted with 23 AYAs (15-29 y/o) explored the effect of a mobile phone app-based intervention on adherence to oral cancer treatment (not OC exclusive). The app included visual and audible medication intake reminders that were tailored to individuals' prescriptions and weekly self-report assessment of adherence and reasons for non-adherence to medication. Adherence was also assessed with MEMS. Forgetfulness was the most reported reason for medication non-adherence in this sample. No

significant effect of the intervention was found in this study. However, the authors noted a higher increase in adherence at post-intervention in participants who were non-adherent at baseline and expressed that it would be of benefit to explore the effect of this intervention in patients who are poorly adherent to cancer medication (Linder et al., 2019).

Evidence on the effectiveness of medication reminders (including those delivered via SMS) in improving OC adherence is lacking. Intervention users have reported the usefulness of reminders as a prompt to take their OC but evidence from RCTs of multi-component interventions is contradictory. SMS medication reminder interventions have shown to improve adherence to medication in chronic diseases. Therefore, this strategy may be an important component of interventions aiming to increase adherence to OC.

A different theoretical approach to the issue of forgetting to take medication states that mobile phone-based interventions only focus on time-based alerts, failing to take into account the individuals' daily routines (Stawarz, Cox, & Blandford, 2014) and that time-based tasks make it more difficult to remember to take medication than routine-based strategies (Park & Kidder, 1996). Routinization consists of finding a routine around the time when medication is due and to associate the routine with the act of taking the medication.

2.5.3. Poor patient education/knowledge about the treatment. Impact on adherence to oral chemotherapy, interventions, and assessment.

Information on the prescribed OC is the starting point for adherence because without the knowledge on how to take their medication correctly patients are not able to follow their prescriptions. Despite this, cancer patients seem to find it hard to remember the information received at their first OC education session and they may need this information to be spread over and reinforced across many consecutive information meetings (Simchowitz et al., 2010).

Poor levels of patient' education has been described as insufficient knowledge about drug-related side-effects and toxicities as well as medication schedules, including the name of the drug. In a systematic review, poor education about OC treatment was found to be the main

nurse/provider-related factor for OC non-adherence (Corrente 2016). Patients with good knowledge about their oral medication treatment (including OAD) show significantly higher levels of adherence than those with poor medication knowledge as it was previously identified in a meta summary of literature about the reasons for oral medication non-adherence (Irwin & Johnson, 2015).

In Australia, findings from a small study (N= 15) showed that only half of OC users remembered the name of their OC and almost half of them did not know their prescribed dose (Griffiths & Pascoe, 2014). A prospective study conducted with 17 AYA OC users (18-39 y/o) in the United States of America, showed that 24% (4/17) of participants did not receive information about storage, handling and disposal of OC, 29% (5/17) did not receive education about drug-drug and drug-food interactions, and a plan on how to manage missed OC doses was not provided to 24% of the sample (4/17). This study also found that knowledge about treatment and disease was commonly reported (88% of the sample) as a facilitator of OC adherence among young people with cancer (Divakaruni et al., 2018).

In a study with 64 patients diagnosed with multiple myeloma and treated with cyclophosphamide, thalidomide, and dexamethasone, most participants self-reported high adherence to the drugs but medication knowledge was found to be low, highlighting a potential threat to adherence. A high proportion of participants (37/64, 57.8%) who reported taking their medication appropriately were not able to identify the correct time for taking the drugs. In-depth interviews with two participants identified their perception of oral cancer treatment as complex. Amongst the study sample, 34.4% of the participants were unfamiliar with the appropriate management of missing a medication dose and three of the participants reported unsafe actions such as taking a double dose when the next dose is due. Moreover, this study found differences in knowledge rates between the three hospital sites, supporting a lack of standardization in patient education (Arber, Odelius, Williams, Lemanska, & Faithfull, 2017).

Although the evidence do not demonstrate the effectiveness of educational interventions alone in increasing medication adherence, multi-component approaches featuring patient education about treatment and other strategies (e.g. medication reminders, cognitive-behavioural strategies) do seem to be effective in enhancing medication adherence in chronic diseases (Spoelstra & Sansoucie, 2015). An example of a successful combination of educational and counselling strategies was seen in a RCT with 86 cancer patients treated with tyrosine kinase inhibitors. The intervention provided tailored patient education including video, booklet, website, and nurse counselling. Education included information about CML, tyrosine kinase inhibitors goals, the importance of adherence, and self-management of side-effects. The intervention group showed higher adherence to the drugs compared to the control group (51% vs 21%, respectively) at nine months, as assessed by MMAS-8 (Kekale et al., 2016).

Similarly, a single-arm study explored the effect of pharmacist monitoring of 23 CML patients prescribed tyrosine kinase inhibitors. Pharmacists contacted participants monthly to assess OC adherence and to provide education about the disease and OC, and the importance of adhering to OC therapies. Adherence in this sample (assessed by self-report) increased from 65.2% to 100% at post-intervention ($p= 0.013$) (Moulin et al., 2017).

The previously described studies did not assess participants' OC knowledge and they focused on medication adherence as the primary endpoint. However, one study which also focused on adherence to OC did report on findings related to OC knowledge. This single-arm study was conducted in 107 participants diagnosed with blood, breast, and gastrointestinal cancers being treated with OC (Muluneh et al., 2018). The pharmacist-led program consisted of education about OC, monitoring of adherence, management of side-effects, and drug interaction. This study found an increase in comprehension of OC treatment from 43% to 95% at post-intervention ($p= 0.005$). Knowledge about OC was assessed through a four-item survey (drug name, patient dosage, drug administration, and recall of at least three adverse

effects) which appeared to be developed for the purpose of the study.

A recent educational program found 17.8% increase in adherence to capecitabine in a sample of 10 non-adherent colorectal and breast cancer patients (Vacher et al., 2019). Adherence was measured by MEMS. The program consisted of an assessment of educational needs, provision of information about treatment's role and mechanism of action, schedule, management of side-effects, management of missed doses, and evaluation of knowledge. Sixty percent of the participants who were non-adherent to OC at baseline were shown to be adherent to their treatment at post-intervention.

The Multinational Association of Supportive Care in Cancer (MASCC) developed the MASCC Oral Agents Teaching Tool (MOATT) as an approach to improve and assess patients' knowledge about OC. This tool includes an initial section focused on the evaluation of OC knowledge with nine questions related to the treatment plan, current medications, and ability to take and access OC drugs. The tool has been used in research and has been found to be highly acceptable to oncology nurses (Rittenberg, 2012). In Australia, an adapted 13-question version of the MOATT was used in the pre-post intervention assessment of patients' and caregivers' levels of knowledge about OC, with an educational intervention that followed the MOATT guidelines (Griffiths & Pascoe, 2014).

The Knowledge Rating Scale (Fonteyn, Spenser, & Gross, 2008) is a scale scored from 0 (no knowledge) to 10 (highest knowledge). It includes questions about knowledge and the ability to take OC, read label information, and side-effects. This tool was used as a pre and post-test measure of participants' perceptions of their knowledge about treatment with erlotinib in a nurse-led feasibility study that aimed to increase knowledge about and adherence to the drug. The intervention consisted of providing education following the MOATT tool and it was found feasible to be implemented in clinical settings (Boucher, Lucca, Hooper, Pedulla, & Berry, 2015).

A patient survey was used to assess knowledge about cyclophosphamide, thalidomide,

and dexamethasone treatment in 64 cancer patients. The survey had 15 questions (13 fixed choice and two open-ended), related to satisfaction with verbal and written information received, which were organized in four sections: confidence in taking OC, knowledge of side-effects of OC, knowledge of when to take OC, what to do if side-effects occurred and what to if a dose of OC was missed (Arber et al., 2017).

2.6. Summary

In this chapter, literature reviews to identify the main modifiable and non-modifiable reasons for OC non-adherence and to compare these findings with those from chronic diseases more broadly, were described. Overall, this chapter identified three main modifiable reasons for OC non-adherence: side-effects, forgetfulness, and poor knowledge about OC.

OC-related side-effects impact negatively on adherence as they can lead to OC dose modification or patient-directed temporary ceasing of treatment, without prior notification to the treating physician. Finding effective ways to manage side-effects, for example, by providing information about how to deal with adverse effects, seems to increase the odds of patients adhering to their OC prescriptions.

Forgetfulness was found to be a common unintentional reason for OC non-adherence and medication reminders have been deemed by OC users as helpful. However, there is a lack of evidence on the effectiveness of these reminders in increasing adherence to OC, which is especially relevant in light of the evidence on SMS-based reminders being effective in improving medication adherence in chronic diseases.

Poor treatment knowledge was found to be a key factor for OC non-adherence which is supported by evidence on sub-optimal knowledge about OC in people with cancer and the need for users to receive more frequent education throughout their treatment. The provision of information about OC as part of multi-strategy interventions has been shown to improve adherence to OC.

The body of knowledge on determinants of OC non-adherence is scarce, compared to

that seen in chronic diseases in general. However, evidence on the main reasons for medication non-adherence in chronic diseases aligns with that of OC non-adherence. The main non-modifiable reasons for OC non-adherence highlighted in this chapter were high out-of-pocket expenses/co-payment, regimen complexity, time since diagnosis/ duration of therapy, and younger/older ages, with no clear cut-off age. Although evidence on age was found to be conflicting in chronic diseases, the rest of the key non-modifiable factors for OC non-adherence appear consistent with those in other chronic conditions.

Effective interventions in increasing OC adherence included multiple components such as written and verbal information about expected side-effects, management and reporting of side-effects, and information about OC treatment. A number of multi-strategy interventions have been tested with positive outcomes on OC adherence, but no intervention has adapted the strategies to be delivered exclusively via SMS, which stood out in Chapter I as the most effective mobile phone platform to provide adherence-enhancing interventions in other chronic diseases. There is also a clear need for interventions that target AYA OC users due to the lack of studies in this age group and their high risk of not following their medication prescriptions. Finally, more evidence is needed on tools to support OC adherence in patients diagnosed with other cancer types, as the main body of knowledge is focused on chronic myeloid leukaemia (CML) and breast cancer.

CHAPTER III. Preferences of AYA and Adult Cancer Patients about the Structure of Elements of a Smartphone Self-Management Program

3.1. Introduction

In Chapter II of this thesis, the need was identified for new interventions to support OC adherence in AYA and adult cancer patients, that integrate multiple evidence-based strategies to address the main reasons for OC non-adherence (side-effects, forgetfulness and poor knowledge about OC). Effective strategies to positively affect the main determinants of OC non-adherence identified in Chapter II were the use of information about the main OC-related side-effects and their management (side-effects), reminders to take OC (forgetfulness), and information about OC treatment (poor knowledge about OC). In Chapter I, SMS was found to be the most popular and effective mobile phone platform to deliver medication adherence-enhancing interventions. In addition to SMS, which is a feature of mobile phones commonly utilized by older generations, smartphones, with internet access, allow medication adherence-enhancing interventions to deliver more detailed information needing larger capacity (e.g. education, videos, audio) to cancer patients, regardless of their geographical location and in real-time. In Australia, the use of smartphones is extensive. In 2016 it was estimated that 84% of the population owned smartphone technology (Deloitte, 2016). Therefore, smartphones are well-positioned as a communication tool with the potential to reach many cancer patients, to provide them with OC adherence strategies of information and medication-intake reminders.

One of the most important strategies to employ in the design of mHealth interventions for cancer patients is the engagement of end-users in the process, as it increases the potential of interventions to be translatable to real health settings and to be accepted by its users (Darlow & Wen, 2016). This is highly relevant to this research, especially in light of evidence that the components of an SMS health intervention can be tailored to patient populations or individuals to increase receptiveness to the messages (Dijkstra, 2008; Kreuter, Strecher, &

Glassman, 1999). According to Muench and Baumel (2017) the digital components of SMS that are thought to be useful to tailor are: a) who sends the SMS, b) how it is sent (which includes the stimulus type e.g. video, text), c) the ideal time of SMS delivery and the frequency of SMS delivery (e.g. daily, twice a day), d) what is sent (which is the actual content of the SMS and includes the SMS target, e.g. to increase OC adherence), SMS structure (e.g. short or long SMS) and the narrative (Muench & Baumel, 2017).

SMS component tailoring is not a common practice in interventions designed to improve medication adherence in chronic diseases in general, and it is usually limited to the content and timing components of SMS. A systematic review of 13 SMS-based interventions to increase medication adherence in chronic diseases (e.g. HIV, schizophrenia, diabetes, coronary heart disease) found that only 1/13 studies used SMS tailored content based on previous qualitative research with end-users, and just 4/13 studies tailored the content to participants' assessments (e.g. adherent vs. non-adherent). Participants were able to select their preferred SMS delivery time in 3/13 interventions and one intervention sent the SMS daily at the time an individual's medication was due (DeKoekkoek et al., 2015). In the oncology context, the two available OC adherence-enhancing interventions that include SMS (described in Chapter IV) only tailored the timing of SMS delivery to participants' OC schedules (Pereira-Salgado et al., 2017; Spoelstra et al., 2016).

This chapter describes a qualitative study that was designed to explore AYA and adult cancer patients' preferences on the structure of elements of a smartphone self-management program to increase adherence to OC. Findings from this study informed the design of the self-management program presented in Chapter V of this thesis.

3.2. Objectives

In this study, the "structure of elements in a self-management program" refers to the arrangement of features of the elements: text message reminders as well as information about OC and symptom management. Preferences on the structure of the self-management program

were defined in this study as the patient's expression of greater liking for certain element features over others.

The objective of this study was to explore the preferences of people affected by cancer on the structure of elements of a self-management program focused on enhancing adherence to OC.

Research question:

What are cancer patients' preferences on the structure of elements of a self-management program focused on enhancing adherence to OC?

Additionally, this study investigates patients' acceptability of a self-management program focused on enhancing adherence to OC.

3.3. Methods

3.3.1. Study design.

This was a qualitative descriptive study (Sandelowski, 2000) that included in-depth interviews with OC users.

3.3.2. Study population.

Recruitment of participants took place between the 1st of December 2017 and the 21st of August 2018. Inclusion of participants into the study followed a convenience sampling approach, according to their accessibility and availability (Elfil & Negida, 2017). Study inclusion criteria were: aged 16-75 years, with a cancer diagnosis, in treatment with OC or took this medication within three years, resides in South Australia, owns a mobile phone with access to the internet, knows how to read text messages, and can read and speak English. This study adopted the Australian Youth Cancer Service definition of AYA as individuals aged between 15 and 25 y/o. Initially, the participants' age limit was 64 years but in the early stages of the study, it was observed that a high number of OC users were older than the age limit, owned smartphones, and were familiar with the use of text messages. Therefore, the age limit was extended to 75 years. The exclusion criterion was the self-reported or suspected

presence of a condition affecting cognitive functions e.g. dementia, psychosis. Conditions affecting people's judgment might limit their ability to understand and answer questions during interviews.

As detailed in Table 1, a total of nine people participated in the study, two AYA (20 years old) and seven adults (50-71 years old), 72% male and 28% female. Recruitment of adolescents into the study was not possible due to the small number of potential participants and only one paediatric recruitment site. Data saturation, defined as the point when additional data does not lead to new themes (Given, 2016) was reached with the sample used. Two additional potential participants were provided information about the study. Both of them were AYAs and declined participation due to not having the time for the study.

TABLE 1

Demographic and treatment characteristics of the sample

Demographic and treatment characteristics (N=9)	**n (%)**
Age (M= 51.44, SD= 19.08)	
Young adults (20 y/o)	2 (22)
Adults (50-65 y/o)	5 (56)
Adults (69-71 y/o)	2 (22)
Gender	
Male	7 (78)
Female	2 (22)
Marital status	
Married/living with a partner	8 (89)
Never married	1 (11)
Highest educational level	
Trade certificate/diploma/TAFE certificate	4 (44)
Finished high school	2 (22)
University degree/diploma	2 (22)
Postgraduate degree	1 (11)
Country of birth	
Australia	7 (78)
New Zealand	1 (11)
Holland	1 (11)
Treatment with OC	
In current treatment	6 (67)
Not in current treatment	3 (33)

Time taking OC/time since last OC dose was taken (in months)	
Time taking OC	2-288 (M=54, SD=116.3)
Time since last OC dose	1-18 (M=13, SD=8.18)

3.3.3. Recruitment and consent of participants.

The study was promoted by the Youth Cancer Services (YCS), Women's and Children's Hospital, Royal Adelaide Hospital, the Queen Elizabeth Hospital, and non-profit organizations (NGO; Leukaemia Foundation, Canteen, and Cancer Voices SA). NGO disseminated the study information through their social media (Facebook, website), and by email to potential participants. Hospital and Youth Cancer Services recruitment was supported by healthcare staff. Potential participants contacted the researcher (Ph.D. candidate) via email/phone or provided written permission to NGO/hospital staff to share their contact information with the researchers.

Before interviews took place, all eligible potential participants received an information sheet and a consent form. This information was sent via email/mail/face-to-face. Consent forms were returned to the researcher in the same way and pre-paid envelopes were provided to participants posting information via mail. Potential participants had a minimum of 14 days to consider their participation in the study before being contacted by the researcher to explore their interest in participating. The researcher discussed the content of the information sheet with potential participants over the phone and helped answer their questions about involvement in the study. Once consent forms were signed, the researcher agreed on a time for a phone interview with the participant. A demographics/selection criteria short questionnaire was completed over the phone, immediately before the interview. The presence of a condition affecting cognitive function (as an exclusion criterion) was discussed with potential participants while reviewing the participant information sheet content. No potential participants were screened out based on these discussions. Study participants received a summary of study findings shortly after the culmination of the study.

3.3.4. Assessment tools.

Data collection consisted of phone interviews. Demographics/selection criteria data was collected through a short questionnaire (Appendix C shows this tool).

Interviews were semi-structured, with open-ended and closed-ended questions that lasted on average for 40 minutes. Interviews were audio-recorded with permission- this was communicated to participants in the information sheet and consent form. The interviews were conducted by the researcher (XSR), a female Ph.D. candidate (psycho-oncology) with 15 years of experience in the support of young and adults with cancer, including research interviews. The interviewer did not have a relationship with the participants before study commencement. Although this study was conducted as part of the interviewer's Ph.D., the risk of interview bias was minimized by the participation of three researchers (KG, IO, and XSR) in the development of the interview script. This script was carefully followed during the interviews. During the interview, participants were asked whether they wanted to obtain a report on the study results once it was published. The interview questions were developed by the researcher with content validation from two experts in the cancer field (oncologist and psycho-oncologist, IO and KG).

The interview consisted of three sections. Topics and questions in section one referred to participants' preferences on components of text messages, section two referred to preferences on the content of text messages, and section three consisted of questions and topics related to motivation to take OC, the structure of the information about OC and side-effects, as well as participants' general acceptance of the program (Appendix D contains the interview script).

3.3.5. Data Analysis.

Data were analysed with assistance from NVivo qualitative data analysis software (QSR International Pty Ltd., version 12). Qualitative analysis was inductive, (by generating knowledge from data collected in interviews), using Braun and Clarke's method of Thematic

Analysis (Braun & Clarke, 2006). This form of analysis involves the examination of patterns within data, from participants' verbal reports of their experience in taking OC and their preferences on intervention delivery. The content of the interviews was transcribed by an external company and was independently reviewed by two researchers (XSR and KG) who identified relevant content that was represented by labels. Codes were also identified and representative quotes were extracted from the transcriptions, with 100% agreement achieved between the researchers after discussions.

3.3.6. Ethics.

The research was approved by the following main Human Research Ethics Committees: the University of South Australia (ID: 200471) and the Women's and Children's Hospital (ID: HREC/17/WCHN/152), and governance authorization was obtained from the Women's and Children's Hospital, the Queen Elizabeth Hospital and the Royal Adelaide Hospital.

3.4. Results

3.4.1. Preferences on components of text messages as oral chemotherapy intake reminders (Part 1).

Delivery platform: conventional text messages preferred over other messaging apps.

All young and older adult participants expressed their preference for conventional SMS over other messaging apps (e.g. Whatsapp) due to their high usability and participants' familiarity with this platform. As a result, SMS was determined to be the most suitable method of delivery.

> "I'm not interested in any more apps than I already use, if that's the question you're asking, so therefore I would prefer it to use an existing SMS, which are on every phone, whereas WhatsApp or whatever the other apps that you're talking about aren't necessarily on every phone" C21 (52 y/o, in OC treatment).

> "Just conventional message I guess… I think it's just easy because I only really use

some other apps for my business. I guess just personally a text message would be more personal than business related" A22 (20 y/o, finished OC treatment).

"As I said, I don't access any apps. I just use the straightforward SMS" D22 (69 y/o, in OC treatment).

Text message sender: who sends the message is not important but perhaps it could be more impactful if sent by someone who is in contact with the treating team. Most of the participants expressed that, to them, it is irrelevant who sends a text message reminder as the SMS would just act as a prompt. However, it was acknowledged that there may be frequent changes in drug doses and prescriptions during OC treatment, therefore someone who is in contact with the treating team and aware of these prescription changes would be in a good position to send the text message reminders.

"It would just be a prompt and I wouldn't mind who would send that" D21 (71 y/o, in OC treatment).

"It would have to be someone that's in contact with my haematologist to know what my current situation is so that does make it hard" C11 (50 y/o, in OC treatment).

Messages based on text only. Most of the participants indicated their preference for text only with no images or videos sent as medication intake reminders because it is simpler.

"Just a text message. It's a very simple process, it just says take your medication. That would remind me. I needn't have a photo or… I can't imagine what photo or video would be appropriate anyway" D21 (71 y/o, in OC treatment).

"If I was wanting a message to be sent to me, it would have to be in writing. Just as simple as possible" A22 (20 y/o, finished OC treatment).

Timing of the messages: as close to time to ideal OC intake as possible. SMS sent close to the due OC intake were considered to be more helpful to participants to remember to take their OC, as an automatic prompt to take their drugs. They expressed that they might forget to take their medication if reminders were sent at a different time of the day or not

daily.

"I take them (cancer tablets) with breakfast and therefore it would be a good time to be reminded at around 7:30 to 8 o'clock in the morning...Just before it's due to prompt me (cancer tablets)… I suppose every morning before breakfast and it would become an automatic prompt for me to take the medication" D21 (71 y/o, in OC treatment).

"So, if it was sent like pretty much on the time I need to take them I'd be like yes, let me go do that now" A22 (20 y/o, finished OC treatment).

"… you get the text message in the morning telling you to take it during the lunchtime, well you might forget between the morning and lunchtime" C22 (59 y/o, finished OC treatment).

The directionality of the text messages: no response required. Preference for the SMS being sent to participants without the need to reply was identified in the interviews. Participants expressed that they did not need additional advice or reporting on their medication intake, as well as not liking the idea of being expected to reply to an SMS.

"There is no need to reply because I don't really like it when I have to reply to messages" A22 (20 y/o, finished OC treatment).

"I think just a reminder would work, in my particular case that would be the only thing that I need is just a reminder. I don't need any other follow-up, just the reminder" C11 (50 y/o, in OC treatment).

Personalization of text messages to include the name of the SMS recipient. A clear preference for messages to be addressed to the recipient, by including their name was identified. It was thought that this would help to avoid the message being read by the wrong person, increase the feeling that the message is sent by a 'real person', and that someone cares about them.

"Maybe just my name and that's it… I just think if you had your name in it it's a real person, so it doesn't feel like an automated message. I'd feel a bit more personal, like

somebody cared" A22 (20 y/o, finished OC treatment).

"I would have a preference for just a name, because I still use names in text messages myself… it's personal preference that people are addressing me, and I address them by name with texts as well… doesn't matter (talking about the name of the medication) that's providing it's clear that the message is about the medication, of course. It doesn't matter if the name is there, it might just say "take your drugs" D21 (71 y/o, in OC treatment).

"Just your name that should be enough, shouldn't it? Because then that alleviates the possibility of a text message going to the wrong person" C22 (59 y/o, finished OC treatment).

3.4.2. Preferences about the content of SMS reminders (Part 2).

Keep messages short and focused. Before the interviews took place, all participants were provided with a list of 24 sample text messages that were written by the research team, based on 12 situations in which chronically-ill patients struggle to take their medications (e.g. when there is no one around to remind them, when they have to travel) (Morisky et al., 2008). The theoretical framework for the sample messages was Banduras' Self-Efficacy Theory (Bandura, 2005) as self-efficacy-based SMS have previously shown to be effective in increasing medication adherence in AYA and adults with chronic conditions (Garofalo et al., 2016; Park et al., 2014). Participants were instructed to choose one preferred message for each of the situations or to provide their ideas for a different message. Most of the participants shared a preference for a standard, short, and focused message that did not relate to specific situations (e.g. travel). Participants stated that SMS technology would not be able to recognize the situation they were experiencing when the message was received. Therefore, situation-related SMS was not found to relevant for reminding participants of their due OC intake.

"I don't see that we need to have a big spiel in any of those blimming (sic) situations. Who's going to know what the situation is? If I'm busy at home, how is a text message going

to change if it knows that I'm busy at home? Your application is not going to know if I'm busy at home or if there's no one around to remind me or if I'm about to leave the house or travel, it's not going to know" C23 (60 y/o, in OC treatment).

"I don't know if the rest is important to anybody, really. The reminder is hey, take your medication, and that should be enough of a reminder to have a serious response from people to take it" D21 (71 y/o, in OC treatment).

"It's time to take your scheduled chemotherapy tablet or please take your scheduled chemotherapy table… I find myself in different situations so if it is-if I find it straightforward and simple you could just keep using that" A21 (20 y/o, finished treatment).

3.4.3. Motivation to take oral chemotherapy, the structure of the information about oral chemotherapy and side-effects, and acceptance of the program (Part 3).

Fear of death and to please family members are key motivators to take oral chemotherapy. Surviving (avoiding premature death) and pleasing their family were the main themes that emerged concerning participants' motivation to adhere to their OC treatment.

"If I don't take them I'll die, it's as simple as that" C21 (52 y/o, in OC treatment).

"I'm motivated because it calms my husband down. That is a factor, I'll be honest" C12 (62 y/o, in OC treatment).

"I guess it was more from mum or dad's comfort, knowing that I'm taking my tablets and I know they're all stressed over that thing" A22 (20 y/o, finished treatment).

Structure of the information about oral chemotherapy and side-effects.

Information sent via SMS should be short, dot points with a link (portable document file/website) to more detailed information. Participants expressed that information about OC treatment and how to manage side-effects is too long to be sent in an SMS. A preference was identified for SMS-delivered information to be short, dot points with a link to a portable document file (PDF) or website. The PDF format was identified by some participants as being useful to store information on the phone to be accessed when needed. They consistently

stated that information on side-effects should focus on the main expected symptoms.

> “I doubt very much one SMS message would be enough text to be able to handle it.” C21 (52 y/o, in OC treatment).

> “Brief. Dot points, you know? Not a lot” C22 (59 y/o, finished OC treatment).

> “If it just had links or something like that to a website that would work as well” C11 (50 y/o, in OC treatment).

> “I guess a general overview of the most common symptoms and, say, how to deal with them or what to do if you get them. And I guess, say, links to more specific information if you need it” A21 (20 y/o, finished OC treatment).

> “So I'd want it like sent to me in a PDF file. I could just download it and I'd always have it" A22 (20 y/o, finished treatment).

> "Maybe I'd make a shortcut on my phone. If I don't read it more than once I could access it regularly to read whatever information I could find" D22 (69 y/o, in OC treatment).

Frequency of information delivery. When asked about their preference on the frequency of delivery of SMS with new information about OC treatment and strategies to manage side-effects, participants’ responses were too heterogeneous (e.g. three times a week, every three weeks, once a month, all at the beginning) to allow the identification of a common delivery schedule preference. This presumably means that the frequency should be tailored to each patient’s preference.

> “I'd probably have the majority of it sent to me in the beginning of this process, and kind of go back and forward to it when I have time or when I wanted to” A21 (20 y/o, finished treatment).

> "Probably just a couple of times a week maybe. Until I know how many I'd have to take, at what time, and I knew what the effects were like at the back of my head” A22 (20 y/o, finished treatment).

"Once a week for three weeks and then once a month or something further on" C11 (50 y/o, in OC treatment).

Acceptability of the program: keen interest in using or recommending the program but somewhat less interest from those with a long history of OC use. Participants expressed their intention to use or recommend the self-management program because of their desire to receive more information on side-effects or OC, its potential usefulness in reminding them to take their OC or their willingness to receive information about side-effects to discuss with the doctor.

"A current daily reminder to take my scheduled chemotherapy pills would be helpful" A21 (20 y/o, finished treatment).

"I can see where it would be a benefit to certain individuals who may not be as rigorous in their tablet taking, I spoke to someone yesterday who mentioned that sometimes he doesn't take his tablet and he feels the effect of it. So, he would benefit from a regular message...If I had known of a program yesterday I would have mentioned it to him" D22 (69 y/o, in OC treatment).

However, some of the participants in treatment with OC for many years expressed that the program may not be of interest to them as they already set a medication-taking routine over time.

"I don't think it would be all that relevant for me now…and that's after 18 years, mind you" D21 (71 y/o, in OC treatment).

"I've pretty much got it under control...I've got a routine going, morning and night go and take the tablets C21 (52 y/o, in OC treatment).

Some participants stated that the information about OC and side-effects may be most valuable to patients starting a new OC prescription.

"If I was starting on something, a different cancer medication in conjunction with this or something that I've not been on and if anyone else is just starting on it, it would

actually be an invaluable thing for them" C11 (50 y/o, in OC treatment).

"Now, how others might manage it would be interesting information, and if you could do that over the first three months, in other words, what had been proved to work for others over that first three months of being on the medication then it should be good" D21 (71 y/o, in OC treatment).

3.4.4. Additional contextual factors to consider.

Oral treatment complexity: cancer treatment may involve a number of oral drugs, not only oral chemotherapy, and a number of other oral medications may also be taken to manage additional chronic conditions. Participants reported the need to take a number of oral medications (in addition to their OC) on a daily basis, which commonly includes those used to manage chronic conditions other than cancer in older participants.

"I take about six different tablets… The prescription ones I take are two different diuretics, an aspirin as a blood thinner. Every Monday and Thursday I take a Bactrim, which is some sort of antibiotic of some description, and I take morning and night doxycycline, which is also an antibiotic" C21 (52 y/o, in OC treatment).

"It used to be seven (tablets) because there were other issues at some point. But now it's back to four again" C23 (60 y/o, in OC treatment).

"Cancer looks nothing, at all, nothing. I've got diabetes, zimaprin (sic), propower (sic)… He's given me some blood – oh what was it? Some Aspirin and blood pressure tablets, just eight" C22 (59 y/o, finished OC treatment).

"I think there was one time when I was on like 28 drugs, I had to try and take those drugs throughout the day" A22 (20 y/o, finished OC treatment).

Forgetfulness is a problem. During the interview, half of the participants expressed that they occasionally forget to take their OC due to being busy, missing their "self-identified prompt" to take OC or not having anyone around to remind them.

"Because sometimes I do forget, mainly because I have to take it with food and I'm

not always regular with my diet. The eating is the trigger to take it, but even then I forget actually sometimes" C12 (62 y/o, in OC treatment).

"I know I got busy but there's the odd time where I'd be busy and I'd forget to take it, and I'd take my medication later than planned too" A21 (20 y/o, finished OC treatment).

3.5. Discussion

A qualitative study was conducted to explore the preferences that AYA and adults with cancer have about the structure of elements in a smartphone self-management program that aims to increase adherence to OC. Nine participants were interviewed and qualitative data analysis enabled the identification of participants' common preferences about most of the explored features. Additional contextual factors emerged from the interviews highlighting forgetfulness as a common issue amongst OC users and the complexity of oral medication schedules for patients being treated with OC. Most of the participants (5/9) were aged between 51 and 64 years with no representation of adolescents in the sample. They were predominantly male (7/9) and there was a range in the length of OC use between two months and 24 years for those in treatment with OC at the time of the interview.

While those OC adherence interventions that include SMS mainly focused on tailoring the timing of SMS (Pereira-Salgado et al., 2017; Spoelstra et al., 2016), this study demonstrated that OC users share common preferences on a wide range of SMS intervention components, which can be tailored to potentially maximize the effect of self-management programs on OC adherence.

Conventional SMS were favoured over other phone messaging apps by all of the participants because of their high usability and familiarity with this platform. Participants did not show a preference for a particular sender of SMS OC reminders but someone who is in contact with the oncology treating team and aware of medication prescription changes would be better positioned to send the SMS reminders. This shows the need for research teams to

establish effective communication channels with treating teams to access information about OC prescription changes, as close in time as possible, to the modifications taking place. The use of text in SMS reminders was the preference of all of the participants as this helps to keep the messages simple. Some participants said that the use of videos or audio recordings would be irrelevant for a medication reminder. This is consistent with the approach taken by most existing SMS medication adherence-enhancing interventions, which are delivered in a text-only format (DeKoekkoek et al., 2015). Participants' preferred frequency and timing of SMS reminder delivery was daily, as close to medication due intake times as possible. This was mainly linked to the possibility of forgetting to take OC if the medication-intake prompt was received too far out from the time of due OC intake. This is in line with the timing of SMS delivery in previous OC adherence-enhancing interventions (Spoelstra et al., 2016)

Participants preferred OC intake reminders to be sent to them with no expectation to reply as they expressed not liking to respond to SMS or not wanting to be monitored (e.g. to provide information on their OC intake). In chronic diseases in general and in cancer treated with OC, the requirement that participants reply to SMS medication-intake reminders has been mainly used as a self-report tool to assess medication adherence or another outcome (e.g. satisfaction), and only in a few cases to provide patient follow-up to medication non-adherence (DeKoekkoek et al., 2015). To our knowledge, there is no evidence of medication adherence benefits to participants who reply to SMS medication intake reminders as confirmation of drug intake.

The name of the SMS recipient was an element participants would like to see in the SMS. This personalization appears to increase the perception that a real person sends the message and that someone cares for them, and it avoids other people reading a message that was not intended for them. Although personalization (e.g. name of the OC, dose) was a feature in one OC adherence-enhancing intervention delivered via SMS (Spoelstra et al., 2016), these elements seemed to be selected arbitrarily without prior evidence that OC users

would accept their inclusion in the SMS reminders.

Participants in the present study had a consistent preference for messages to be short, concise, and standard to all OC users at all times. This was an unexpected study finding. A list of 24 theory and evidence-based sample messages was developed by the research team and provided to participants for them to select their preferred messages from, or to suggest their message ideas to help address each of the 12 situations in which chronically ill patients are known find it difficult to take their medications (Morisky et al., 2008). Participants consistently expressed that the situations were not relevant to SMS OC reminders because SMS technology cannot determine the situation participants will be experiencing when the message is received. Additionally, the pre-written messages were deemed to be too long and participants preferred the reminder SMS to be simple and short.

The two consistent motivations for participants to follow their OC prescriptions were the fear of premature death or will to survive, and/or to give their family members (e.g. parents, partner) the reassurance and relief that they are taking their OC.

Information about OC and strategies to manage its related side-effects was found to be considered too long to be sent in a conventional text message. Participants suggested that this information should be short to fit an SMS and that larger amounts of content could be delivered via SMS hyperlink to enable accessing a PDF document or a website. One of the advantages of having access to this information in PDF format (versus the website option) identified by participants is that it offers the opportunity to store the content on their smartphones for future consultation or printing.

Participants' preferences on the ideal frequency of delivery of information about OC and side-effects management were too heterogeneous to identify a common schedule (e.g. three times a week, every three weeks, monthly, all at the beginning). This shows the need for participants to be individually asked about their preferred information delivery frequency before the commencement of an intervention of this type.

The concept of a smartphone self-management program to support adherence to OC was well-accepted by participants who consistently expressed they would use it or recommend it to other OC users. Some of the patients with a longer history of OC use verbalized that the program may not be useful to them as they had already established routines to take their medication. On the other hand, the self-management program was evaluated by some participants as being highly valuable to patients who were newly prescribed OC drugs, as they require new routines for medication intake to be set and lack knowledge about their OC prescriptions and how to manage the expected side-effects.

An additional factor related to the context in which patients take OC was the complexity of their oral medication schedules. This complexity refers not only to cancer-related treatment (e.g. steroids, antibiotics, OC) but is also due to the need to incorporate OC drug schedules into treatment for other chronic conditions. These multi-medication complex schedules require patients to develop the ability to handle a large number of drugs at different times of the day. Finally, some participants referred to forgetfulness as a common issue leading to occasional missing of OC doses. This is due to not having anyone around to remind them to take the medication, being busy, or missing their usual trigger (e.g. meal) to take their OC.

3.6. Limitations and directions for future research

The study sample had an underrepresentation of women and most of the participants were aged 51-64 years old, with no adolescent representation.

Nonetheless, the engagement of OC users in formative research with the purpose of informing the design of self-management programs (one of which was later trialled) is an important contribution. This is best practice in the design of mobile phone-delivered health interventions for cancer patients (Darlow & Wen, 2016), and behaviour-change interventions more broadly (Yardley, Morrison, Bradbury, & Muller, 2015).

To our knowledge, this study is one of the first SMS medication-adherence studies in

which end-users' preferences have been considered on a wide range of SMS components that can be tailored to individuals or populations, to potentially increase the impact of the intervention. It makes an important contribution by identifying common preferences amongst OC users and those features that need individual tailoring, to inform the future development of mobile phone interventions that are relevant to and adopted by users.

Finally, this study highlights OC users' preferences about the structure of elements of an OC adherence-enhancing intervention, intended to be delivered exclusively via mobile phone text messages. Findings will serve as a guide to inform the design of other OC adherence interventions and medication adherence in other chronic diseases.

3.7. Conclusions

OC users' preferences about the structure and features of a smartphone self-management program that aims to enhance OC adherence were identified by this study. Tailoring the identified elements may enhance the relevance and usability of the tool to the studied population. Findings from this research helped to inform the design of a smartphone self-management program, described in Chapter V of this thesis.

CHAPTER IV. Mobile-Based Oral Chemotherapy Adherence-Enhancing Interventions: Scoping Review

4.1. Overview of Paper 2

The gap in the provision of optimal monitoring of OC adherence for cancer patients has been identified as an issue, especially in light of evidence on high rates of OC non-adherence (up to 54%) (Greer et al., 2016). The dangerous health-related consequences of not following OC prescriptions make it imperative to provide cancer patients with tools to support their OC adherence. In Chapter I of this thesis, it was identified that mobile phones were well-positioned to deliver effective medication-adherence interventions in other chronic diseases (e.g. diabetes). However, little was known about available mobile phone-based tools to support cancer patients in taking their OC as prescribed.

This scoping review was conducted to:

Explore what is known about mobile phone–delivered interventions designed to enhance adherence to OC.

Examine findings on the utility of mobile phone–delivered interventions in increasing adherence to OC, and

Identify opportunities for the development of OC adherence–enhancing interventions via mobile phone in the future.

In the context of this thesis, the research outlined in Paper 2 helped to identify knowledge gaps and inform the design of the smartphone program that was trialled at a later stage. The high acceptability, usability, and reported dearth of available mobile phone-based OC adherence-enhancing interventions set the need for the design and evaluation of the self-management program in this thesis. In Chapter II of this thesis, it was recommended that OC adherence interventions should include strategies to address the three main reasons for OC non-adherence (forgetfulness, side-effects and poor knowledge about OC) and Chapter III, reported the preferences OC users have for adherence-enhancing interventions being

delivered exclusively via SMS, due to users' familiarity with this tool and its high usability. None of the available interventions that utilized SMS in the scoping review included strategies to positively modify all the three main reasons for OC non-adherence. Finally, no interventions described in the paper targeted AYA who, due to their developmental stages, may be at a higher risk of OC non-adherence than younger and older cancer patient populations. These knowledge gaps provided an opportunity to design a novel SMS-based tool to support AYAs and adults with cancer to follow their OC prescriptions.

One study meeting the criteria for inclusion in the review was made available after Paper 2 was published. This was a randomised controlled proof-of-concept trial of a smartphone-based game with 76 adult female participants diagnosed with metastatic breast cancer and treated with OAD (OC or hormonal therapy). The intervention group (n=36) used the mobile game for three weeks and the control group (n=40) was provided with written information about the management of side-effects and individual oral medication. Consistent with findings from Paper 2, this study focused on the two most common strategies observed amongst mobile phone-based health interventions that aim to increase adherence to OC: information about drug-related side-effects and their management, and medication intake reminders (alarm). Also, in consonance with findings in Paper 2, in which studies reported the interventions to be highly usable, acceptable, and feasible, this study reported high users' satisfaction with the intervention. Acquisition of information, usefulness in managing side-effects, and helpfulness in taking medications were reported by 61% of the participants. More than half of the participants found the game difficult to use but detailed information about these issues was not detailed in the paper. Like a number of studies included in Paper 2, this study did not use or failed to report on the design or theoretical frameworks informing the intervention. In terms of the utility of the mobile game in increasing short-term adherence to OC, the study found significantly higher adherence to OAD (self-report) in the intervention versus the control group (adherence mean 7.6 versus 6.5 respectively, $p = < 0.001$). Paper 2

highlights the importance of user engagement in the design of mobile phone-based health interventions. It is not clear if stakeholders were involved in the development of the mobile game. However, the study is a proof-of-concept trial of the intervention which suggests that findings may serve to inform future refinements of the mobile game based on data collected from users (H. J. Kim et al., 2018).

Kim et al.'s study (2008) is the first to use smartphone-based game technology to increase adherence to OC. However, it did not address any of the knowledge gaps highlighted in Paper 2 and summarized in this overview.

Appendix E contains this paper's supplementary file describing the included studies.

4.2. Paper 2

Review

Mobile-Based Oral Chemotherapy Adherence–Enhancing Interventions: Scoping Review

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Abstract

Background: Adherence to oral chemotherapy is crucial to maximize treatment outcomes and avoid health complications in cancer patients. Mobile phones are widely available worldwide, and evidence that this technology can be successfully employed to increase medication adherence for the treatment of other chronic diseases (eg, diabetes) is well established. However, the extent to which there is evidence that mobile phone–based interventions improve adherence to oral chemotherapy is unknown.

Objective: This scoping review aims to explore what is known about mobile phone–delivered interventions designed to enhance adherence to oral chemotherapy, to examine the reported findings on the utility of these interventions in increasing oral chemotherapy adherence, and to identify opportunities for development of future interventions.

Methods: This study followed Arksey and O'Malley's scoping review methodological framework.

Results: The review search yielded 5 studies reporting on 4 interventions with adults (aged >18 years) diagnosed with diverse cancer types. All interventions were considered acceptable, useful, and feasible. The following themes were evident: text messages and mobile apps were the main methods of delivering these interventions, the 2 most commonly employed oral chemotherapy adherence–enhancing strategies were management and reporting of drug-related symptoms and reminders to take medication, the importance of stakeholders' engagement in intervention design, and the overall positive perceptions of delivery features. Areas for future research identified by this review include the need for further studies to evaluate the impact of mobile phone–delivered interventions on adherence to oral chemotherapy as well as the relevance for future studies to incorporate design frameworks and economic evaluations and to explore the moderator effect of high anxiety, poor baseline adherence, and longer time taking prescribed drug on adherence to oral chemotherapy.

Conclusions: Despite the increasing body of evidence on the use of mobile phones to deliver medication adherence–enhancing interventions in chronic diseases, literature on the oral chemotherapy context is lacking. This review showed that existing interventions are highly acceptable and useful to cancer patients. The engagement of stakeholders as well as the use of a design framework are important elements in the development of mobile phone–delivered interventions that can be translated into oncology settings.

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KEYWORDS

medication adherence; antineoplastic agents; neoplasms; cell phone; text messaging; mobile apps; review; mHealth

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Introduction

Background

The widespread increase in the use of chemotherapy delivered via the oral route is transforming oncology. However, self-administration of oral chemotherapy encompasses a number of challenges for patients and health professionals to ensure adequate management of adherence and toxicities [1]. Nonadherence can reduce treatment efficacy and lead to dangerous health complications, including death [2]. The rates of adherence to oral antineoplastic agents can be as low as 46% [3]. Despite this fact, most health institutions do not practice standardized patient monitoring procedures for adherence [4].

Adherence is defined as the extent to which a persons' medication-intake behavior corresponds with the agreed recommendations of the clinician [5]. Adequate oral medication adherence is also important for the optimal treatment of other chronic conditions (eg, diabetes and HIV). Due to the long-term nature of these diseases, adherence and monitoring are required over long periods, which can be problematic. Technology is increasingly being used to help chronically ill patients adhere to their treatment regimens [6]. Mobile phones are a technological platform that allows delivery of behavioral interventions, assessments, and real-time data collection [7] and, importantly, can also facilitate access to support patients who, due to their remote geographical location or limited mobility, cannot access face-to-face services. Mobile text messages (short message service, SMS) and mobile apps are 2 types of mobile phone–based technology that are most commonly used to support patients with chronic diseases [6].

Worldwide availability of mobile phones is extensive and ownership of these technologies will continue to grow. As a result, there is great potential to use mobile technology to improve health care delivery. In 2016, 62.9% of the world population (4.65/7.40 billion) owned a mobile phone and this figure is set to increase to 67% (5.16/7.71 billion) in 2019 [8]. The introduction of smartphones means that mobile phones are no longer limited to being a tool for calls and text messages but also allow internet connectivity. Mobile devices (including smartphones and tablets) are currently the main source of internet connection. In 2017, approximately three-fourths of the worldwide internet access occurred through mobile devices [9]. In Australia, in 2016, 84% of the population (approximately 16 million people) owned a smartphone. The only places in the world where uptake of smartphones is greater are South Korea, the Netherlands, and Norway [10].

Previous research has already established that interventions delivered via mobile phones can significantly improve medication adherence for people with arterial hypertension [11], heart failure [12], and diabetes [13,14]. Moreover, acceptability and usefulness of mobile phone–delivered interventions are known to be high among chronically ill patients [6]. However, it is important to note that the efficacy of adherence-enhancing interventions is determined by the quality of the strategies delivered by a form of technology. Gains should not be simply attributed to the type of technology employed.

Although the reach, popularity, and many technological features of mobile phones now mean they are ideal platforms to provide health care support to cancer patients undergoing oral chemotherapy, because the widespread use of oral chemotherapy drugs is relatively new, the extent to which evidence is available to support this strategy is unknown.

Objectives

To address the emerging issue of oral chemotherapy nonadherence, this scoping review aims to:

- explore what is known about oral mobile phone–delivered interventions designed to enhance adherence to oral chemotherapy,
- examine the reported findings on the utility of mobile phone–delivered interventions in increasing adherence to oral chemotherapy, and
- identify opportunities for future development of oral chemotherapy adherence–enhancing interventions via mobile phone.

Methods

Overview of Methods

The scoping review methodological framework used in this review was outlined by Arksey and O'Malley [15]. This approach is ideal to understand research fields that are in early stages because it allows the rapid mapping of key concepts, sources, and evidence available, leading to identification of gaps in the existing literature [15]. This method aims to produce broad results from all relevant literature instead of trying to answer highly focused questions from specific study designs, as is the case in systematic reviews. Consistent with Arksey and O'Malley's framework [15], this study presents a narrative review of literature based on an analytic framework (thematic analysis) [16] and does not seek to assess the quality of studies, including risk of bias or generalizability of findings.

Identification of Relevant Studies

A structured database search was conducted in April 2018 with the following databases: MEDLINE, EMBASE, EMcare, and PsycINFO using terms related to 5 key areas: mobile phones, adherence, intervention, oral chemotherapy, endocrine therapy, and cancer. Subject headings and keywords used in databases and independent reviews were collated for each of the 5 key areas using the "OR" function and groups 1 to 5 were connected with the "AND" function. Examples of keywords included in each area were (1) mobile phone, text messaging, mHealth, mobile app; (2) patient compliance, medication compliance, medication adherence; (3) program, pilot, study, review, randomized controlled trial; (4) oral chemotherapy, antineoplastic agents, oral anti-cancer, endocrine therapy; and (5) neoplasm, tumour, cancer. Subject headings (eg, Medical Subject Headings) were employed. English language limits were applied, but no date restrictions were used for this search. Grey literature was searched through the ProQuest Dissertations and Theses database, limited to doctoral theses between January 2013 and March 2018 due to the high number of irrelevant results obtained with unlimited searching. To extend the results, an independent search in a Web journal took place. Reference

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lists of relevant articles were also reviewed for references that may have been missed when conducting the database research.

Conference proceedings were included to make this review as broad and informative as possible. Titles and abstracts of retrieved documents were screened against inclusion criteria, followed by full text review of relevant studies.

Selection of Studies

To include relevant studies and associated content that contributed to meeting the objectives of this review, the following inclusion criteria were used to guide the screening process: (1) research-based studies on interventions that aim to increase adherence to oral chemotherapy or endocrine therapy, (2) targets cancer patients taking oral chemotherapy or endocrine therapy, (3) use of mobile phones as a main tool to deliver the intervention, and (4) articles written in English. In this study, adherence was defined as taking oral chemotherapy in accordance with the dose and frequency prescribed by the clinician.

Data Charting

Full text articles were assessed to extract relevant information, and this was transferred into an Excel spreadsheet. Information charted in this process was as follows: (1) authors, (2) study purpose, (3) research design (eg, qualitative and randomized controlled trial [RCT]), (4) participants (age, cancer diagnosis, oral chemotherapy or endocrine treatment, and country), (5) mobile phone features (eg, text messages and apps), (6) intervention (duration and key components of intervention), and (7) main findings (summary of the most relevant findings, including recommendations for future studies). A second reviewer assessed 50% (5/10) of articles to ensure validity of information extraction.

Thematic Analysis and Reporting of Results

Following the methodological framework from Arksey and O'Malley [15], thematic analysis [16] was used to identify what is already known about mobile phone–based oral chemotherapy adherence–enhancing interventions, the utility of interventions in improving oral chemotherapy adherence, and the opportunities for future development in this area. A second reviewer assessed all codes and a complete agreement was achieved. Due to the research designs used in the reviewed studies (most were nonexperimental), results are reported in category groups conformed by common themes in the reviewed literature. Categories are aligned with the aims of this research.

Results

Overview of Results

During the initial database search, 43 articles were retrieved. After removal of duplications, 29 unique publications were identified. Titles and abstracts were scanned for relevance against the inclusion criteria and those that did not match (eg, focus on another illness or lack of focus on improving oral chemotherapy adherence) were removed, leaving 10 articles for full text review. After full text review, 6 articles were excluded. An additional publication was added following an independent review in an online journal. No articles fitting the inclusion criteria were identified through the grey literature search in the ProQuest Dissertations and Theses database or through search in articles' reference lists (Figure 1 shows the detailed process of screening and inclusion). Ultimately, 5 articles [17-21] reporting 4 interventions were included in this review, 2 of which were abstracts from conference proceedings and 3 were peer-reviewed journal articles. Moreover, 1 study [19] describes the development of an intervention that was later tested in another one of the included articles [18]. Multimedia Appendix 1 shows the information extracted.

Search results showed that research on mobile phone–based interventions to increase adherence to oral chemotherapy began in 2015. The research designs of the studies were qualitative (3 out of 5 studies) [19-21] and experimental RCTs (2 out of 5 studies) [17,18]. All but 1 study explored the feasibility and acceptability of interventions, and 2 out of 5 studies used an RCT design to evaluate the effect of mobile phone interventions on adherence to oral chemotherapy [17,18].

Moreover, 3 out of the 5 studies had small samples (5-32 participants) [19-21]; the remaining 2 studies used an RCT design with larger samples (80 and 181 participants) to measure oral chemotherapy adherence as a primary outcome [17,18].

Of the 5 studies, 3 included participants with diverse types of cancer [17-19], 1 focused on patients with chronic myeloid leukemia [20], and 1 focused on breast cancer patients [21]. All the studies focused on adult participants (aged >18 years).

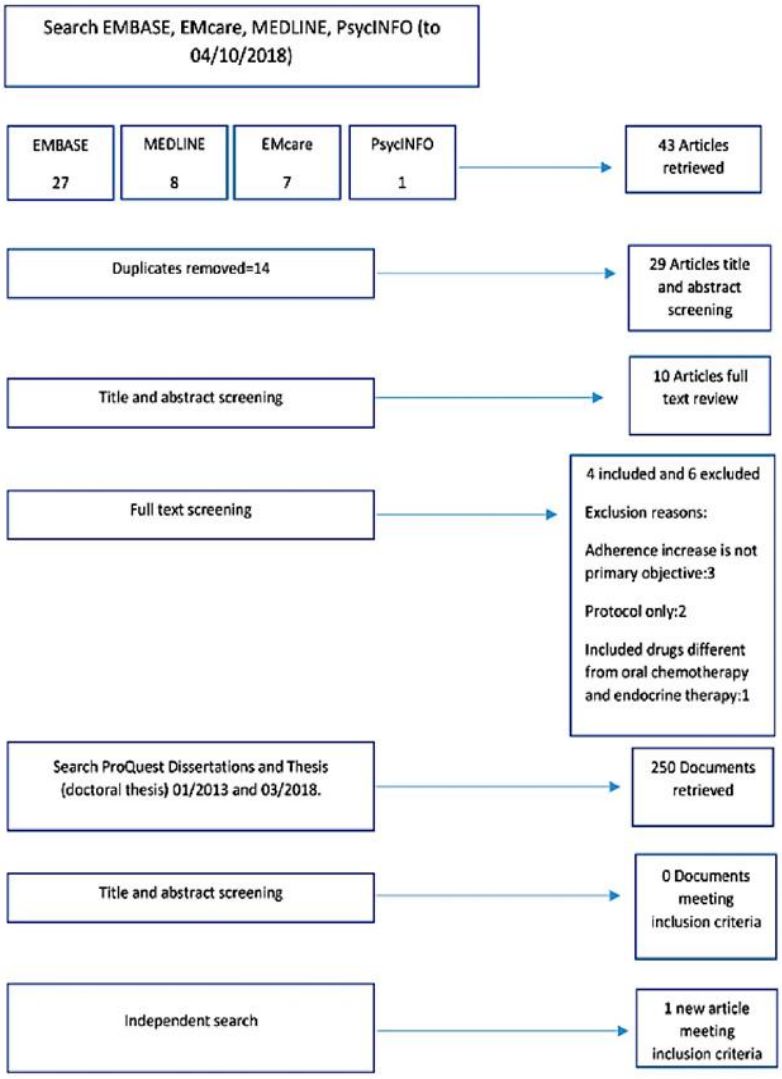
Strategies and Features of Intervention Delivery

Various methods of delivery and adherence-enhancing strategies were employed in the reviewed studies. In addition, 2 distinct methods were used to deliver the interventions: SMS text messages and mobile apps. The SMSs were sent as medication intake reminders and frequency was daily or twice daily according to individual medication intake schedules [17,20]. The SMS reminders were bidirectional (participants' response "Y" or "N" was expected) to collect data on the frequency of taking medication. The content of the SMS (message bank, wording, and theoretical framework) was reported by Spoelstra et al [17] and informed by social cognitive theory. The SMS content in Pereira-Salgado et al's study was not described [20]. For future research to understand the process of how SMS reminders influence adherence, it is important that these details (eg, content, frequency, and sender) are reported. Overall, participants showed high rates of response to SMS reminders. In 2 studies, they replied 87.13% (1036/1189) of the times [17] and only up to 22% (17/80) of the SMS were not replied when sent [20]. This not only shows that participants received and read the SMS but also actively participated in reporting medication-taking events.

The SMS reminders in the study by Pereira-Salgado et al were part of an intervention that also included a Web-based app. It recorded participants' side effects and severity and provided real-time self-management advice [20]. This intervention also incorporated nurse-led phone support consultations. This last strategy was not necessarily delivered via mobile phone.

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Figure 1. Flowchart of study selection process and included studies.



Mobile apps were used as delivery features in 2 interventions [18,21]. They all included reminders to take medication. Daily reminders (alarms) were set by users according to their preferences in 1 study [19]. Brett et al's study did not report on any characteristics of medication reminders (eg, frequency and type) [21].

Other strategies used in mobile app interventions were real-time side effect management advice, cancer-specific information, medication-specific information, and chat forums (Table 1 shows features and strategies of each of the interventions). Automatic generation of reports accessible by research teams was another technical element in 1 mobile app and a combined Web app and SMS intervention. Reports contained data on symptom severity [19] or a combination of medication-taking and symptom severity [20].

The potential influence of oral chemotherapy-induced side effects on adherence to oral chemotherapy was recognized widely in the reviewed studies. Strategies to improve symptom management were incorporated in three-fourths of the interventions. These strategies included symptom reports with real-time reception of tailored feedback [18,21] and symptom recording in a side effect mobile app diary [21]. Symptom burden and severity was also 1 of the primary outcomes in most interventions (3 out of 4 studies) [17,18,20].

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Table 1. Strategies and features of interventions.

Strategy or feature	Spoelstra et al, 2016 [17]	Greer et al, 2017 [18]	Pereira-Salgado et al, 2017 [20]	Brett et al, 2018 [21]
Strategy				
Medication reminders	□	□	□	□
Symptom management information	—[a]	□	□	□
Cancer-specific information	—	□	—	□
Individual nurse phone support	—	—	□	—
Medication-specific information	—	□	—	□
Recording of side effects	—	□	□	□
Chat forum	—	—	—	□
Feature				
SMS[b] text messages	□	—	□	—
Mobile app	—	□	—	□
Web-based app	—	—	□	—

[a]Strategy or feature not present.

[b]SMS: short message service.

Acceptability, Usability, and Feasibility of Interventions

Overall, all interventions reviewed were found to be acceptable and useful, and their implementation was feasible. The definition of acceptability differed across studies. Spoelstra et al's study defined acceptability as the percentage of patients who agreed to take part in the study and the percentage of patients who completed the study [17]. This SMS medication reminder intervention had high rates of acceptability among cancer patients, with 75.7% (78/103) of eligible potential participants consenting to participate and 86% (42/49) of the initial participants completing the entire intervention.

Preliminary acceptability of ChemOtheRapy Assistant (CORA) mobile app [19] was described as the result of a 5-stage developmental process that led to intervention improvement. Stakeholders (eg, patients, and oncology clinicians) participated in qualitative research to provide information that led to the design of an acceptable final version of the mobile app.

Pereira-Salgado et al's REMIND system study assessed intervention acceptability by interviewing participants (patients and nurses) after using the system [20]. The intervention was highly acceptable to participants in terms of its content, timing, and perceived utility of each component (SMS medication reminders, symptom management advice, and nurse phone support). Usability was assessed separately in this study with participants expressing appreciation for the ease of use of text reminders and the weekly symptoms component, with the exception of a small number of participants who expressed delays in receipt of the SMS. The nurses also found the intervention useful but suggested changes to the number of report emails and layout of the intervention manual (ie, inclusion of tabs to facilitate the search for specific content).

The definitions of acceptability and usefulness in Brett et al's study were not provided [21]. This conference proceeding indicated that participants considered individual components of the mobile app intervention (information section, links to evidence around adjuvant endocrine therapy, side effects diary, and repeat prescription reminders) acceptable and useful. However, perceptions of the usefulness of the chat forum were mixed. Participants also suggested more information on side effect management strategies.

Measures of feasibility also varied across studies. Measures included the number of SMS delivered and returned [17] and possibility to implement and integrate the intervention into a clinical setting [20]. Brett et al's study, which aimed to explore the feasibility of a mobile app intervention, reported results in terms of high acceptability, usefulness, and usability of the intervention [21]. The CORA exploratory study [19] did not report on the intervention feasibility. However, its later implementation in clinical settings with 181 oral chemotherapy users can be considered confirmation of feasibility [18].

Stakeholders' Engagement in the Design of Interventions

Stakeholders' engagement was evidenced in the design of all the reviewed interventions, through the exploration of end users' perceptions of the acceptability and usefulness of mobile phone interventions. An example of this is the design of the CORA mobile app, which was informed at every stage by groups of stakeholders: patients and caregivers; oncology clinicians; cancer practice administrators; and representatives of the care system, community, and society [19]. Engagement of these groups allowed the intervention to be shaped by users' opinions on the need for oral chemotherapy self-management support; the role of the intervention in supporting oral chemotherapy

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self-management, acceptability, and usability; as well as exploring possible implementation barriers [19].

Cancer patients also participated in early design phases of Pereira-Salgado et al's REMIND system for patients with chronic myeloid leukemia [20] and Brett et al's mobile app for women taking adjuvant endocrine therapy after breast cancer [21]. The first study also included oncology clinicians and explored their perceptions of the nature, extent, and reasons for nonadherence to tyrosine kinase inhibitors. The second study examined patients' preferences on the content of a mobile app [21]. Findings from both studies informed the strategies incorporated into mobile phone interventions, in line with patients' needs and preferences.

Spoelstra et al's study [17] assessed, among other variables, participants' acceptability and satisfaction with the intervention, and both were rated as high by study participants. These findings support the possibility of cancer patients to incorporate this text message intervention into their daily lives.

Design Framework Informing Development of Mobile Phone Interventions

Overall, 2 of the 4 interventions [19,20] reported the use of a design framework as a guide during the development process. In the design of the CORA mobile app [19], the investigators incorporated Whittaker et al's framework [22], which sets a process that involves steps to develop and test mobile phone–based health interventions. In doing this, the investigators based the design on a theoretical model, conducted formative research, pretested the intervention with stakeholders, and piloted the app with 5 participants enrolled in the next phase of the research, which was an RCT. Results from the experimental phase were reported in a separate study [18], and qualitative follow-up was also intended to be measured in the same study. However, due to the nature of the article (conference proceeding), detailed information on this was not provided.

Fishbein et al's CORA exploratory study [19] compared their intervention development process (a posteriori) with recommendations highlighted by Darlow and Wen's review [23], which recommends the adoption of 8 practices in the development of mobile phone interventions. In addition to the steps described above, user testing was conducted via qualitative methods, adequate time needed to test technology was anticipated, stakeholders were engaged in all steps of the intervention design, usability of the app to ensure the technology was simple and intuitive was assessed, the intervention's promotion of a sense of competence over patients' own care was explored, health professionals were consulted to ensure the use of the mobile app was not a burden to them, and the results of development and testing phase were published.

Schofield and Chambers's framework [24] specifies 7 features for the development of effective, clinically feasible, and sustainable interventions: (1) targeting cancer type and stage, (2) tailoring to unique individual needs, (3) promoting self-management, (4) efficient intervention delivery, (5) ensuring evidence-based and theoretical grounding, (6) specifying protocol training and adherence, and (7) confirming stakeholder acceptability. All the previously described steps were followed in the design of Pereira-Salgado et al's REMIND system study [20].

The importance of using a theoretical grounding in the design of mobile phone interventions was highlighted by this review. Murray et al's conceptual model [25], which provides a description of multidimensional factors affecting medication adherence, was used to inform the strategies used by the CORA mobile app [19]. Self-determination theory informed the use of motivational interviewing as part of the nurse phone support strategy in Pereira-Salgado et al's REMIND system study [20]. Self-determination is a theory of motivation that emphasizes the importance of supporting individuals' natural tendencies to exhibit healthy behaviors [26].

Social cognitive theory [27], more specifically self-efficacy, guided the content design of the SMS messages in Spoelstra et al's intervention [17]. According to the authors, messages were written using motivational content to stimulate the participants' engagement with SMS and behavior change. In Pereira-Salgado et al's REMIND system study [20], motivational interviewing provided as part of the nurse support was designed to stimulate participants' self-assessment of the problem as well as to help provide them with the information, resources, and skills needed to achieve oral chemotherapy adherence. The authors indicated that the nurse phone support strategy appeared to increase self-efficacy according to the analysis of participants' interviews, but this was only assessed qualitatively.

Utility of Mobile Phone Interventions in Increasing Adherence to Oral Chemotherapy

Due to research designs employed by the reviewed studies and the aims of this scoping review, numerical comparisons are not offered. This section provides a narrative approach to describe findings on the observed utility of mobile phone interventions in improving adherence to oral chemotherapy.

The 2 experimental studies in this review (Spoelstra et al's study and Greer's et al's CORA experimental study) [17,18] did not find statistically significant differences between the experimental and control groups. However, findings point toward patient and treatment variables (high levels of anxiety, poor baseline adherence, and length of treatment), which may moderate the effect of interventions on oral chemotherapy adherence. Participants who reported adherence problems at baseline showed better adherence after using the app than the standard care group (as measured by Medication Event Monitoring System) [18]. This study also found that participants with high levels of anxiety in the experimental group showed better adherence to oral chemotherapy than the standard care group at the end of the study (measured by Morisky Medication Adherence Scale). Spoelstra et al's study [17] found that participants in the experimental group showed better adherence than the control group in later weeks of the study (measured by SMS reply self-report).

Pereira-Salgado et al's REMIND system study described participants' perceived utility of the intervention in increasing adherence to tyrosine kinase inhibitors [20]. Most participants reported that reception and response to SMS reminders stimulated their medication adherence due to accountability (eg,

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reinforcing habits at the beginning of treatment or drug intake support during time of routine change).

Although qualitative studies [19-21] were not designed to evaluate the effect of interventions on medication adherence, they constitute a necessary step in the development of acceptable, usable, and relevant interventions, which were also found useful to participants in supporting their oral chemotherapy intake.

Issues and Limitations Related to the Use of Mobile Technology

Failure to receive up to 40% of SMS on time was experienced by 2 out of the 9 participants who completed Pereira-Salgado et al's study because of slow networks in rural areas [20]. Technological difficulties and being without their mobile phone (eg, left at home and losing phone) were reported by some participants. These barriers seem difficult to overcome and should be taken into consideration at the time of designing interventions using mobile phones.

One limitation found in the use of the CORA mobile app [19] was the need to send symptom reports to clinicians via email instead of using the electronic health record system due to regulations. This method did not guarantee that clinicians would open the report emails when sent. Another limitation of the app was the support of only iPhone and Android phones, excluding other operating systems. The authors recognized the potential to include other smartphone operating systems to reach a broader population of smartphone users.

Brett et al's study did not describe limitations and issues related to the use of their mobile app [21]. This study was a conference proceeding, which can explain reduced information about the topic.

Discussion

Principal Findings

This scoping review brings together the available evidence on adherence-enhancing interventions delivered via mobile phone in the context of oral chemotherapy. A total of 5 studies describing 4 interventions met the inclusion criteria. This low figure may be because the widespread use of oral chemotherapy is a relatively new medical advancement, and the extended access to mobile phones, especially smartphones, is also a recent phenomenon, which can also explain the young data of studies in this area.

Consistent with trends in other chronic diseases [6], this review shows that the 2 main features used to deliver mobile phone interventions aiming to increase oral chemotherapy adherence are SMS and mobile apps. Regardless of the technology feature employed, all interventions explored were highly acceptable, useful, and feasible to be implemented in clinical settings.

Despite the variety of adherence-enhancing strategies in the interventions, 2 strategies were common to most studies: drug-related symptom management advice and reporting and medication-intake reminders. This approach is compatible with evidence on drug-related symptoms and forgetfulness as the 2 main barriers to oral chemotherapy adherence [33]. It is important to notice that although all the reviewed interventions primarily addressed adherence barriers related to the patient (forgetfulness, knowledge of therapy, and condition) and the therapy (side effects), only half of those interventions took into account health care team and system-related barriers (communication with treating team, monitoring of adherence, and side effects). Strategies to address these barriers consisted of reports on the presence and severity of side effects and adherence frequently sent to treating teams to stimulate prompt communication and adequate monitoring of oral chemotherapy treatment as required [18,20].

The relevance of patients' involvement in the design, implementation, and evaluation of health research has been widely recognized [34]. The use of a participatory research model allows generation of more significant research questions, alignment of intervention goals with end users' needs, increase in the acceptability and usability of health interventions, and enhancement of translation of findings into real-life settings. This was acknowledged by most studies in this review whose intervention strategies were shaped by stakeholders' perceptions of barriers to adherence, need for self-management support, or their preferences on components of the interventions. It was also generally recognized that interventions need to be found to be acceptable, useful, and usable to stakeholders before moving toward experimental research phases.

This review showed that there were no established processes for the development of mobile phone health interventions. Some researchers did not use or at least did not report the utilization of a mobile phone intervention design framework, including theoretical grounding. Following a framework to design mobile phone–based adherence-enhancing interventions in the oral chemotherapy context supports the development of acceptable interventions that are of intuitive and relevant use to cancer patients. Overall, the use of design frameworks can help to adequately plan the resources needed in each stage of the design as well as to canalize these assets into tools that can be successfully implemented in oncology settings.

Mobile phone health intervention design frameworks in this review also highlight the need to develop interventions based on a theoretical approach. This is crucial as technology alone cannot be seen as a strategy to increase medication adherence. Although most reviewed studies reported a theoretical framework informing their design, some inconsistencies were found in the explanation of the theoretical elements of the interventions, for example, the use of the term "motivation" alone to describe self-efficacy-informed SMS content or intervention strategies. According to Bandura's self-efficacy theory [27], individuals' levels of motivation are heavily based on their beliefs in their capacity to display behaviors that will impact events affecting their lives. Therefore, motivation alone may not be enough to explain the influence of self-efficacy-based interventions on medication adherence. Moreover, in the context of self-efficacy theory, patients' success in adhering to oral chemotherapy is the most effective source informing patients of their ability to follow their drug prescriptions. It is crucial for self-efficacy-based interventions to describe the process through which self-efficacy (as a

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construct influenced by multiple elements) is expected to support cancer patients to achieve adherence to oral chemotherapy. Without this explanation, motivation remains an isolated variable that cannot be linked to self-efficacy.

Overall, general perceptions of mobile phone technologies in this review were positive. As an example, SMS had high rates of delivery and response success, presenting this mobile phone feature as one that is able to be successfully implemented in clinical settings. However, the use of SMS and other mobile phone features encompass challenges that are not easy to overcome. Patients who live remotely, with poor internet or phone coverage, are prone to miss medication reminders or experience issues accessing mobile apps. Patients may also lose their mobile phones or leave them at home, missing the opportunity to benefit from real-time interventions at times. At the time of reporting results related to adherence-enhancing interventions delivered via mobile phones, it is important for authors to describe strengths, limitations, and barriers in the use of mobile phone technology. This will help to inform future researchers on the obstacles and advantages of delivery features when designing interventions of this type.

A strength of this review is its novelty as it is the first study to examine the current state of knowledge about oral chemotherapy adherence–enhancing interventions delivered via mobile phones and to identify opportunities for future research in the area. Another strength of this study is the use of a methodological framework for scoping reviews, which increases consistency and structure of the search process and reporting of findings. In addition, reliability of the search strategy was increased by involving a research librarian in the process.

Limitations

Scoping reviews include a variety of study types to answer broad research questions by mapping available evidence and identifying knowledge gaps. The purpose of scoping reviews is not to ask highly focused research questions or to assess the quality of the reviewed literature, as is the case in systematic reviews. Due to the variety of research designs in the reviewed studies, quantitative analyses on available data were not possible.

The search strategy in this study was limited to research published in English, which may have led to the omission of other sources of information.

Furthermore, this review was able to incorporate and analyze only those studies available at the time of the search that fit the inclusion criteria. Our search yielded results showing 1 study protocol that despite meeting most of the inclusion criteria, was not research-based at the protocol stage [35].

Opportunities for Future Research

This review provides evidence of the scarcity on studies that evaluate the effect of mobile phone interventions on adherence to oral chemotherapy. Mobile phone interventions in this review were highly acceptable and useful to oral chemotherapy users. Therefore, there is a need for future research to take the next steps into experimental studies to generate evidence-based knowledge that has the potential to be translated into oncology settings.

In other chronic diseases, the use of SMS medication reminders has proven to be effective in increasing medication adherence [28]. It would be useful if future studies carefully described the key elements of SMS reminders used in interventions (eg, content, frequency, and sender) so that researchers are able to determine which elements are most likely to have an impact.

It is possible for SMS reminder interventions to incorporate content grounded on evidence-based theoretical models that encourage behavior change. In addition, due to internet accessibility, use of smartphones enables text message interventions to deliver not only medication reminders but also larger contents of information addressing additional barriers to oral chemotherapy (eg, education).

Despite a general failure of studies to report cost-effectiveness analysis of mobile phone adherence tools [6], the design of these types of interventions may involve elevated costs in time, human, and financial resources. Due to this consideration and the need for adherence-enhancing tools to be translatable to real oncology settings, future research could benefit from following a mobile phone health intervention design framework and the inclusion of economic analysis.

According to the World Health Organization, patients in developing countries face a number of health care barriers (eg, short staffed hospitals, lack of patient access to care, and long waiting times to see a doctor) [29], which may increase the chances of oral chemotherapy nonadherence. It is estimated that in developing countries in 2015, one-third of people owned a smartphone, and this figure is set to increase to approach the ownership rates in developed countries in the next few years [30]. Studies in this review focus exclusively on patients living in developed countries. It would also be useful to explore the impact of such interventions in developing countries.

Although the scope of this review was not limited to adults, the body of literature included in this study only targeted cancer patients older than 18 years. Evidence shows that adolescents and young adults are at higher risk of oral chemotherapy nonadherence than younger and older users [31]. The use of mobile phones among adolescents and young adults is even higher than that among adults. In Australia, in 2015, 9 in 10 teenagers (aged 14-17 years) owned a mobile phone [32]. Therefore, it is important that future research also addresses the nonadherence of younger oral chemotherapy users via mobile phone–delivered interventions.

More studies on the moderator effect of anxiety, poor baseline adherence, and length of treatment would be beneficial to understand the role those variables play on oral chemotherapy adherence interventions delivered via mobile phone.

Conclusions

This review shows the lack of research on oral chemotherapy adherence–enhancing interventions delivered via mobile phone. Available interventions, delivered via SMS and mobile apps, are highly acceptable and useful to oral chemotherapy users, and nonadherence in this group is a serious issue. These findings support the need for the development and evaluation of mobile phone tools to assist cancer patients to follow their oral chemotherapy prescriptions. This review also highlighted the

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importance of stakeholders' involvement and the use of a design framework in the development of mobile phone–based interventions aiming to support oral chemotherapy intake to increase translatability into real oncology practices. Given the increasing use of oral chemotherapy and the widespread availability of mobile phones worldwide, further research in this field is expected to rapidly increase in the near future.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Included studies.

[PDF File (Adobe PDF File), 280KB - mhealth_v6i12e11724_app1.pdf]

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Abbreviations

CORA: ChemOtheRapy Assistant
RCT: randomized controlled trial
SMS: short message service

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CHAPTER V. Development of a Smartphone Program to Support Adherence to Oral Chemotherapy in People with Cancer

5.1. Overview of Paper 3

The key modifiable reasons for non-adherence to OC as well as the need for the development and trial of a smartphone-based tool that includes these key factors were established in previous chapters of this thesis (Chapter II and Chapter IV respectively).

This paper includes the above-mentioned evidence and reports on the development process of the smartphone program based on two methodological frameworks: Whittaker et al.'s development and evaluation framework for mHealth interventions (Whittaker, Merry, Dorey, & Maddison, 2012) and the Behavioral Intervention Technology (BIT) model (Mohr, Schueller, Montague, Burns, & Rashidi, 2014). The use of these types of frameworks was identified as best practice in chapter IV of this thesis.

The design and evaluation of mobile phone-based interventions involve considerable amounts of time, human and financial resources and the final tool should be able to be integrated into real oncology settings where healthcare professionals oversee administration. The importance of making intervention development studies like this publicly available, to inform the scientific community about the methodology involved in the design of the tools, has been previously highlighted (Darlow & Wen, 2016).

In the context of this thesis, Paper 3 describes the research conducted and the theoretical and methodological frameworks used in the design of the smartphone program. The proof-of-concept trial of this program is described in the next chapter (Chapter VI). This study may also serve to inform the development of future mobile phone-delivered interventions to support OC adherence.

Appendix F contains this paper's supplementary file showing modifications to the Symptom Management Toolkit.

5.2. Paper 3

Patient Preference and Adherence

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METHODOLOGY

Development of a Smartphone Program to Support Adherence to Oral Chemotherapy in People with Cancer

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Purpose: To describe the theoretical, evidence-based and consumer-informed development of a smartphone self-management program aiming to support adherence to oral chemotherapy in adolescents and adults diagnosed with cancer.

Methods: The design of the program followed two frameworks for the development and evaluation of mHealth interventions and was conducted in three steps: 1) conceptualization, which involved an extensive literature review and a scoping review that led to the identification of the behavioral change strategies in the program; 2) definition of features and structure, based on a formative study with end-users to explore their preferences about the structure and elements of the program; and 3) selection of program delivery technology, whereby available technology platforms were examined and the most suitable tool to deliver the program was selected.

Results: Three main reasons for oral chemotherapy non-adherence were identified: forgetfulness, side-effects and poor knowledge about oral chemotherapy. Key behavior change strategies were also identified, namely, medication intake reminders and information about oral chemotherapy and managing side-effects. Based upon end-user feedback the method of delivery of these behavioral strategies that was deemed most appropriate was conventional text messages. The reminders were standard, short, text-only messages sent when each oral chemotherapy dose was due, one way (no need to reply) and addressed the end-users using their first name. Delivery of information about oral chemotherapy and side-effects was tailored to each individual's preferred frequency.

Conclusion: The careful design process described in this paper may serve to inform the development of future mobile phone-based medication adherence-enhancing interventions for people with cancer. A trial to explore end-users acceptability of and satisfaction with the intervention is currently underway.

Trial Registration: ACTRN12618001987257p.

Keywords: oral chemotherapy, medication adherence, mobile phone, smartphone, text messages, cancer

Background

Oral chemotherapy (OC) drugs are increasingly being used in cancer treatment which allows patients and caregivers more independence in drug administration outside of hospital settings. However, these people with cancer are faced with the challenge of being responsible for self-managing their chemotherapy intake under less medical supervision. OC non-adherence can lead to health complications, including death.[1] Despite this, disturbing rates of non-adherence to OC (up to 54%) have been found among adults with cancer.[2] In adolescents and young adults

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aged 16–25 y/o (AYA), OC non-adherence rates are yet to be established, but there is evidence of low medication adherence in AYA diagnosed with other chronic diseases such as human immunodeficiency virus, asthma, rheumatoid arthritis, epilepsy and diabetes mellitus.[3–5]

Adherence is defined as the extent to which a person's behavior in taking medicines corresponds with the agreed recommendations of the clinician.[6] Although evidence on the minimum adherence rates required for the majority of OC drugs to achieve optimal outcomes is scarce, an adherence threshold of 80% or more has been consistently used in medication adherence research.[7] One of the main challenges faced by OC users and oncology health professionals is the lack of standardized oncology practices to monitor and support OC adherence.[8] This highlights the need to make self-management tools available to people prescribed OC, in order to ensure that the way they take their medication is consistent with their doctors' recommendations. Due to evidence on low medication adherence in AYA with chronic medical conditions, this population may have an even greater need for OC adherence support programs than other age groups.

Given their widespread popularity and sophisticated features, mobile phones are proving to be promising tools to deliver medication adherence interventions to people with chronic diseases.[9] However, evidence on the effect of mobile phone-based interventions on OC adherence is lacking.[14]

An intervention to support OC adherence should be suitable for integration into "real" oncology settings and suitable to be administered by existing, busy healthcare professionals. The design and evaluation of mobile phone-based health interventions involves considerable time, human and financial resources. Therefore, it is important that research on these types of interventions includes input from end-users and follows a standardized process to increase the chances of the intervention being efficacious and acceptable.[10] Experts recommend that researchers facilitate public access to the development process of mHealth interventions to enable other investigators to understand the methods involved in the design.[11] mHealth has been defined by the World Health Organization as the use of mobile devices (mobile phones, patient monitoring devices and other wireless technology) to support medical and health practices.[12]

mHealth Frameworks

In this study, two mHealth frameworks were used to guide the development of a novel smartphone text message program to support adolescents and adults with cancer in taking their OC as prescribed by their doctor: the Behavioral Intervention Technology (BIT) model[13] and Whittaker et al's development and evaluation framework for mHealth interventions.[10]

Whitaker et al's development and evaluation framework for mHealth interventions[10] was created to increase the understanding of best practice in the design of such interventions. This was in response to the lack of dissemination of formative research and intervention design studies prior to publication of most randomized controlled trials in mHealth. The framework recommends six steps: conceptualization, formative research, pre-testing, pilot study, randomized controlled trial and qualitative follow-up.

Further, the integration between behavioral and technological aspects of interventions is essential in the development of behavioral tools delivered via mobile phones and the internet that aim to achieve health-related goals through the use of evidence-based methods. This premise is the essence of the BIT model.[13] The BIT model has two levels, the theoretical level which involves setting the clinical aims of the intervention or articulating "why" it needs to be developed, as well as the behavioral strategies needed to achieve the aims or the conceptual "how" of the model. The second level is known as the instantiation level. Instantiation is a term used in computer programming and involves the identification of concrete actions needed to deliver more general categories of strategies previously established (e.g. text message medication reminders as a behavioral change prompting strategy). This level refers to the elements of the intervention or the "what"; the technical details of how the elements are displayed (e.g. delivery mediums such as video, text, etc.) and the workflow of the elements in the intervention that determine exactly when each element will be deployed.

Purpose of the Study

The creation of the program outlined in this paper addresses the aforementioned pressing need for OC users to be supported in self-managing drug administration. It builds upon the promise shown by mHealth in improving adherence to medications for the treatment of other chronic diseases[9] and addresses the dearth of evidence on the efficacy of mobile phone-based interventions in increasing adherence to OC.[14] More specifically, this paper describes the first phase in the development of a smartphone text message self-management program to support adherence to OC in adults and adolescents affected

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by cancer. It consists of three steps: conceptualization of the program, definition of the features and structure of the program and selection of the technology used to deliver the program. Acceptability and satisfaction with the intervention will be explored in a pilot proof-of-concept trial which is currently underway.

Step 1. Conceptualization of the Program

This step led to definition of the clinical and usage aims of the program and identification of behavioral change strategies incorporated into the intervention in order to achieve its objectives. In order to do this, an extensive literature review on key reasons for OC non-adherence that have the potential to be modified by a mobile phone-based intervention was conducted. This was followed by a scoping review that explored what was known about available mobile phone-based interventions to increase adherence to OC, the reported usability of those interventions and opportunities for future research (see[14]).

The selection of behavioral change strategies was also guided by evidence showing that medication adherence is a multi-factorial phenomenon, which makes it difficult to generate a matrix of determinants to predict individual medication adherence.[15] Therefore, this intervention should focus on addressing multiple variables that effect adherence behavior.

Methods

A database search of Medline, Embase, Emcare and PsychINFO was conducted to find systematic reviews on determinants of non-adherence to OC. Inclusion criteria for this search were: a) follow a systematic review approach, b) containing reasons/determinants/factors for oral chemotherapy/oral endocrine therapy non-adherence, and c) be written in English. The search started with systematic reviews because they account for methodical revisions and reports on existing evidence up to the last date searched. The most recent systematic review was published in 2016 and covered evidence until June 2015.[2] Two additional systematic reviews were found[7,16] and were included in the review. In order to add more recent evidence to this review, a second database search was conducted for a) research-based studies, b) containing reasons for oral chemotherapy/oral hormonal therapy non-adherence, c) written in English and d) published between June 2015 and March 2018. Two relevant studies were identified[17,18] and incorporated into the literature review.

Three main reasons for non-adherence to OC (with the potential to be modified by a mobile phone-based intervention) were found to be: 1) forgetfulness, 2) side-effects and 3) poor knowledge about oral chemotherapy. An in-depth examination into the reviewed studies facilitated selection of behavior change strategies that had been found to be useful in addressing the key barriers to OC adherence, with no evidence on their previous integration into a text message-based program for OC users. Table 1 summarizes these key reasons and corresponding behavior change strategies.

Findings from the second review in this step (scoping review) have been published elsewhere.[14] The review identified five papers reporting on four interventions. The interventions, delivered via mobile phone short message service (SMS), commonly known as text messages, apps or a combination of both, were deemed by their users as highly acceptable and usable. The review highlighted a lack of SMS-based interventions incorporating strategies to address the three previously identified key reasons for OC non-adherence and the scarcity of mobile phone-based interventions to support AYA in adhering to their OC prescriptions. The importance of following a development framework for mHealth interventions and engaging end-users in intervention development were also highlighted by the review.

Table 1 Key Reasons for Oral Chemotherapy (OC) Non-Adherence and Potentially Effective Behavior Change Strategies to Address Barriers

Main Reason for OC Non-Adherence	Reference	Potentially Effective Behavior Change Strategy	Reference
Forgetfulness	[7,16,18]	Text message-based medication intake reminders (evidence only in other chronic diseases)	[19]
Side-effects	[2,16–18]	Information to manage challenges related to side-effects (evidence on its effectiveness only as part of multi-strategy interventions)	[18,20–23]
Poor knowledge about oral chemotherapy treatment	[7,16]	Information about OC treatment (evidence on its effectiveness only as part of multi-strategy interventions)	[18,20,24]

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Step 2. Definition of the Features and Structure of the Program

This step consisted in the identification of the technical elements (eg, notifications, messaging, reports) included in the program in order to deliver the behavior change strategies to users.

The technical characteristics of the intervention (eg, the platform used to deliver the strategies, personalization of the strategies) and the frequency and conditions of intervention delivery (eg, frequency of medication reminders) were defined in this step. The selection of the program's features and structure was informed by findings from a formative study (conducted by the research team) which explored patients' preferences about the structure and elements in a smartphone self-management program to support adherence to OC. This study is outlined in the following paragraph. The most suitable sources and structure of information to be incorporated into the program were identified through a literature review.

Methods

Nine people diagnosed with cancer, who had experience taking OC, were involved in the formative qualitative study. Data were collected via semi-structured phone interviews. Participants were aged 20–69 years, 78% male and 22% female, and treated for diverse cancer types in South Australian hospitals. Sixty-seven per cent of the participants were in active treatment with OC and 33% had their last OC dose up to 18 months before the study commenced. Data were analysed using Thematic Analysis.[25] Data saturation was reached for most of the topics explored.

Findings included that participants preferred a short standard SMS medication reminder, delivered via conventional mobile phone SMS (instead of other messaging apps such as Facebook messenger and Whatsapp). This SMS should be consisting of text-only, one-way communication (no need for users to reply) which was personalized with their first name. Information about OC and side-effect management was deemed by the participants to be too long to be sent in a conventional SMS, which only allows for 160 characters. There was a preference for these strategies to be delivered by an SMS hyperlink to a Portable Document Format (PDF) file. Participants' preference for their OC intake reminder SMS was 15 mins before the OC dose was due. Since OC schedules vary between individuals, it became apparent that the timing of SMS delivery needed be tailored to each individual's medication prescription.

The formative study did not find consistency in OC users' preferences on the frequency of delivery of information about OC and side-effects management. These findings suggest that tailoring the frequency of delivery for both strategies to individual end-users' preferences may be the most suitable option. Study participants were asked to provide examples of what they would like their SMS reminders to say. These examples allowed the creation of the following standard SMS: "Please take your oral cancer medication now. If you need further support, let us know and we will be happy to help (name and phone hospital contact)".

In addition to the formative study, procedures were undertaken to help define the program's content structure. The content of the strategy "information about oral chemotherapy" was an extract from the education section of the eviQ website (www.eviq.org.au), which is a national resource of evidence-based cancer treatment protocols and was recommended to the research team by oncology healthcare professionals (clinicians and nurses) in five Australian hospitals. In this step, the guidelines for drug-specific education in the MOATT (Multinational Association for Supporting Care in Cancer MASCC Teaching Tool for Patients Receiving Oral Agents for Cancer)[26] were used to determine the availability of information on the eviQ website and the content that needed to be incorporated from other information sources. This process led to the definition of the structure of the content of the "Information about oral chemotherapy" strategy that served as a guide for posterior development of tailored information to each end user's OC prescription. Table 2 shows the content present and not present on the eviQ website according to MOATT's guidelines.

The content in the "information about managing side-effects" strategy was informed by a literature review (conducted by the research team) in which the Symptom Management Toolkit[27] was identified to be potentially effective in reducing the presence and severity of symptoms in patients taking OC. Due to the length of the tool (93 pages) and the American English employed, the Toolkit was reviewed by an experienced oncologist (IO) and two research psycho-oncologists (XSR, KG) to adapt its structure to be mobile phone-friendly, relevant to Australian OC users and suitable to the purposes of the self-management program. Some of the toolkit's characteristics were deemed by the reviewers to not be suitable for the purposes of the program (see Supplementary file).

Step 3. Selection of Program Delivery Technology

Together with step 2, this step aimed to answer questions related to the technical elements of the program defined as

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Table 2 Information on the EviQ Website Patient Education Section, Based on the MOATT Guidelines for Drug-Specific Education

Information	MOATT Guidelines	Information Present in eviQ Website	Information Not Present in eviQ Website
Drug name	To provide generic and trade drug name	Generic name	Trade name
Drug dose and schedule	To provide information about: What the drug looks like How many different pills are to be taken? How many times a day should be taken? For how long should it be taken?	How many different pills are to be taken How many times a day should be taken? For how long should it be taken?	What the drug looks like
Where to store pills or tablets	How should I store it? To be specific, for example away from the heat (not in the kitchen), away from humidity (not in the bathroom), away from the sun (not under a window)		How to store medication
Potential side effects and how to manage them	To include information about potential side-effects and how to manage them. Also to include lab evaluations or any medical tests that will be used for drug monitoring	Potential side effects and how to manage them	Lab evaluations or any medical tests that will be used for drug monitoring
Any drug or food interactions	Is it safe to take it with other drugs, food, vitamins, herbs, supplements, or other treatments I use?	General drug, herbs and medication interactions. Information on what to report to the doctor	
When and whom to call with questions	To provide information on how the patient can get in touch with treating team if having trouble late at night or on the weekend	Information on when to go to emergency and what information to collect from their treating team.	Hospital-specific emergency contact details

Note: Data from Kav et al.[26]

the "how" (technical) instantiation component in the BIT model.[13]

The fit between the available technology options and the practical demands of the program guided the selection of the most appropriate technology for program delivery. The program requirements were to be accurate in SMS delivery at the date and time intended, to allow automatization of SMS delivery, to offer high levels of security to protect users' contact details, to allow data entry does that not pose a time burden and to be cost-effective (in order to increase the chance of translation into real oncology settings). To meet these demands, a solution consisting of an automated SMS gateway (a platform that allows pre-scheduling of the SMS and delivers them automatically) was considered ideal. Two options were compared: an information technology (IT) solution developed specifically for the purposes of the program and available secure websites. Table 3 shows a comparison between the two options.

The comparison between the two SMS technology options showed that while both alternatives seemed to be accurate in SMS delivery and highly secure, available secure websites had the following advantages over the tailored IT solution: saving development time, avoiding the possibility of system issues requiring specialist IT support, and a lower cost. Therefore, this option was selected and explored further by testing two websites that appeared to meet the practical demands of the program. After a one-month trial of the two websites, one of them showed issues with SMS delivery accuracy, consistently delivering SMS at the wrong time, so this option was eliminated.

Google Drive (an online file storage system) was employed to save information about OC and side-effects in PDF format. Google Drive is secure (password-protected), free of charge and document hyperlinks can easily be shared via SMS.

Results

The three steps previously described allowed the development of a smartphone text message self-management program to support adherence to OC in adolescents and adults with cancer.

The clinical aim of the program was to support users to maintain or increase their OC adherence rates at a level equal to or higher than 80% (percentage of OC prescribed doses/OC doses taken) during the time of program delivery. The usage aim

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Table 3 Comparison Between a Tailored Information Technology Solution and Available Secure Websites for Delivery of Text Messages in the Program

Technology Characteristics	Tailored IT Solution	Available Secure Websites
Cost (Au$, based on 3500 SMS)	9000–13,000 (total cost of SMS Au$ 287 included)	287 (0.082 per SMS)
Time	3 months development-solution may present fails needing IT support, less researchers' time required for manual data entry as a database is linked to the SMS gateway	No time to develop- slightly more researchers' time required for data entry as website is not linked to an external database.
Security (confidentiality terms and security software packages)	High	High
Accuracy (SMS delivery at the intended time and day) SMS automatization	High Yes	High Yes

of the program was defined as end-users' high acceptability of and satisfaction with the program. Behavioral change strategies that may positively impact on three key reasons for OC non-adherence were defined and categorized according to Michie et al's Behavior Change Technique Taxonomy[28] which provides a consensual structure to report behavior change interventions. These behavioral strategies are:

- Prompts: medication intake reminders sent via text messages, to reduce forgetfulness in taking OC doses. Category 7.1[28]
- Instruction on how to perform the behavior: information about strategies to manage OC-related side-effects, to reduce symptom severity. Category 4.1[28]
- Instruction on how to perform the behavior: information about individual OC treatment, to increase knowledge about OC. Category 4.1[28]

The features of the program were identified based on findings from the formative qualitative research described in Step 2 of this paper. Table 4 schematizes the structure of the program based on the BIT model.[13]

Proof-of-Concept Trial of the Program

A pilot, proof-of-concept trial of the intervention described in this paper is currently being conducted at six Australian hospitals. All relevant ethics and governance approvals were obtained. Australian New Zealand Clinical Trial Registry number (ACTRN): ACTRN12618001987257p. The aim of the study is to explore whether participants' find the intervention acceptable and whether they are satisfied with it. The study was designed as a 10-week non-randomized trial with participants aged 16–75 years, receiving OC (non-endocrine) drugs, who own a smartphone and are willing to receive and read SMS

Table 4 Structure of the Program Developed Based on Evidence and Formative Research, According to the BIT Model

Instantiation Component	What	How (Technical)	When
BIT Component	**Elements**	**Characteristics**	**Workflow**
Intervention component	(a) Reminders to take medication (b) Information about oral chemotherapy (c) Information about managing side-effects	(a) Standard (text-only) reminders to take medication delivered via SMS. SMS are one-way (no need to reply) and personalized with users' name (b) Information delivered in SMS hyperlink to PDF online document (c) Information delivered in SMS hyperlink to PDF online document	(a) Delivered 15 mins before due oral chemotherapy dose intake. Frequency tailored to individuals' prescription. (b) Delivered at the frequency pre-selected by each individual (c) Delivered at the frequency pre-selected by each individual

Note: Data from Mohr et al.[13]

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texts. Adherence to OC is being assessed through medication event monitoring devices (MEMS) and a self-report questionnaire. Other endpoints of the study are: knowledge of oral chemotherapy, the occurrence and severity of symptoms and satisfaction with the intervention. Participants' socio demographic data are also being collected. Findings from the trial will determine the feasibility of the intervention, as well as further refinements needed to progress to a randomized controlled trial.

Discussion

The development process of a novel smartphone self-management program that aims to support oral chemotherapy (OC) adherence in adolescents and adults was described. The program's design addresses two main gaps: the lack of mHealth interventions to support adherence to OC and the scarcity of these types of interventions to support AYA in adhering to their OC prescriptions (likely to be an at-risk group).[14]

The design was informed by evidence that forgetfulness, side-effects and poor knowledge about oral chemotherapy are the key reasons for OC non-adherence that have potential to be modified by a mobile phone-delivered intervention. Also, it was recognised that that SMS reminders to take OC, as well as information about oral chemotherapy and its side-effects, are potentially effective strategies to address the factors determining non-adherence. Whittaker et al's model[11] provided a methodological framework for the design of the program, and the BIT model[13] provided a theoretical structure for program development.

Oral chemotherapy users were also engaged in the design process via formative research, in which their preferences about the structure and elements of program were explored. This is particularly important as the final objective of an intervention of this type (once its efficacy has been established) is that it is highly accepted by its end-users and translatable into "real" oncology settings. Should the proof-of-concept trial show that the program is useable, it could easily be made available to help people with cancer to adhere to their OC schedules as the system is easy and cost-effective for health professionals to use.

Importantly, oncology healthcare teams (clinicians, nurses and pharmacists) from five out of six of the Australian hospitals were engaged at all steps of the development by providing their feedback and suggestions about the structure and content of the program. Healthcare teams' suggestions shape the design of the intervention. For example, they suggested eviQ as the most suitable and reliable information source for OC treatment and they informed the research team about the characteristics of OC schedules which helped in making decisions about individual tailoring of the frequency of SMS reminders to take medication and the content of information in the program.

The design of the program took approximately one and a half years. However, this is an iterative process as the current pilot proof-of-concept trial (underway) will provide additional information on possible further program refinements that may improve acceptability and user satisfaction.

The program's trial involves a heterogeneous sample of patients with various cancer types and OC drugs. Additionally, while a number of intervention features are set to be tailored to the user (eg, time of drug intake, frequency of delivery of SMS with information), other features are general to all users (eg, content of SMS reminders) or users taking specific drugs (information about oral chemotherapy and side-effects). Findings from the proof-of-concept trial will inform the suitability of the program to different cancer types and OC drugs and, if available, areas of opportunity for tailoring of additional intervention features will be highlighted.

This paper addresses' experts' recommendations to make contributions to the literature that detail the development process of mHealth interventions.[11] The process described here could be used to guide the methodological design of future OC adherence interventions delivered via mobile phones.

Limitations and Directions for Future Research

The formative study which informed part of the program's design used qualitative methods. While data saturation was reached for most of the topics explored and findings may serve as a reference for the design of future-related research, intervention-specific formative research is highly encouraged. A limitation of this study is that, although the literature reviews conducted in the design process described were extensive and systematic, their findings do not discriminate between studies with poor methodology or with restricted generalization of findings, as it is the case in systematic reviews that use more rigorous methodology.

One of the strengths of the design process described in this paper is its potential to be highly relevant to end-users and be translatable into oncology settings. The program was developed based on evidence, it was informed by theoretical

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and development mHealth frameworks, and importantly, end-users and oncology health professionals were engaged in the process. Additionally, this program addresses gaps in the literature such as the unavailability of SMS-based interventions that incorporate strategies to manage the key reasons for OC non-adherence and the scarcity of these types of interventions for younger people with cancer.[14]

It has been suggested that the development and evaluation (including a randomized controlled trial) of mHealth interventions takes between three and four years to be completed.[10] This may be too long for interventions based on technology, which evolves rapidly affecting the usability of the tools. In order to keep up to date with technology changes, it is recommended that the evaluation of interventions incorporate qualitative methods to explore further refinements including changes in the technology platforms used.[10] The development of this program took longer than was initially planned (six additional months) due to challenges in the recruitment of participants to the formative research. Similar delays may be also experienced in the pilot proof-of-concept trial of the program. It is important for future research to take into account the time span involved in the creation of mHealth interventions and adequately plan for it.

The design process described in this study may inform the development of future mobile phone-delivered interventions to support OC adherence.

Conclusions

This study described the development process of a smartphone text message self-management program to support OC adherence in adolescents and adults with cancer. Evidence about gaps in the literature, the main reasons for OC non-adherence and strategies to positively affect those factors, as well as mHealth design and theoretical frameworks informed the process. Oral chemotherapy end-users and oncology healthcare professionals were engaged during the design to increase the odds of the program being accepted by end-users and translatable into oncology settings. A proof-of-concept trial is now being conducted to explore whether the intervention is acceptable to adolescents and adult OC users and they are satisfied with the outcomes.

Ethics Approval and Consent to Participate

The formative research was approved by the following Human Research Ethics Committees: Womens' and Children's' Hospital (HREC/17/WCHN/52) and the University of South Australia and Central Adelaide Local Health Network (South Australia). Participants provided written informed consent and the study was conducted in accordance with the Declaration of Helsinki.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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CHAPTER VI. A Smartphone Program to Support Oral Chemotherapy Adherence in Young and Adult People with Cancer: Proof of Concept

6.1. Overview of Paper 4

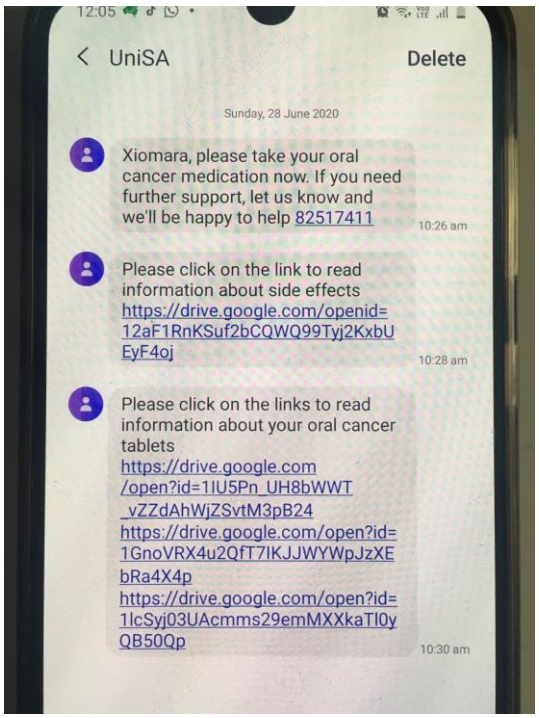
Paper 4 describes the proof-of-concept trial of the smartphone self-management program to support adherence to OC in AYA and adults with cancer.

This study was essential to the body of research in this thesis as it allowed identification of OC users' high acceptability and satisfaction with the smartphone self-management program, the design of which was informed by evidence described in previous chapters of this thesis. A larger RCT is needed to evaluate the effect of the program on adherence to OC. This study also highlights the intervention and methodological refinements that need to be considered before conducting a larger trial.

Study participants received SMS with reminders to take their OC and links to information about their OC and information about management of the five most common side-effects for their OC. Figure 1 provides examples of SMS in the smartphone program.

Figure 1

Examples of SMS sent to study participants



The study was approved by the following Human Research Ethics Committees: The Women's and Children's Hospital (ID: HREC/18/WCHN/146), Calvary Health Care Adelaide (ID:18 CHREC F010), The University of South Australia (ID: 201826), Central Adelaide Local Health Network (ID: SSA/19/CALHN/150), and Metro South Hospital and Health Service (ID: SSA/19/QMS/51343). Trial registration number: ACTRN12618001987257p.

Participants were recruited at six public and private hospitals in Adelaide, South Australia (Royal Adelaide Hospital, Queen Elizabeth Hospital, Women's and Children's Hospital, Calvary North Adelaide, and Calvary Central Districts Hospitals) and one public hospital in Brisbane, Queensland (Princess Alexandra Hospital).

6.2. Paper 4

Skrabal Ross, X., Gunn, K.M., Suppiah, V., Patterson, P., Boyle, T., Carrington, C., Tan, S., Ryan, M., Joshi, R. & Olver, I. (2020). A smartphone self-management program to support adherence to oral chemotherapy in people with cancer: proof-of-concept trial. Submitted 15 May 2020 to the Research in Nursing and Health journal (under review).

A smartphone self-management program to support adherence to oral chemotherapy in people with cancer: proof-of-concept trial

ABSTRACT

Non-adherence to oral chemotherapy (OC) can lead to health complications, including premature death. Mobile phones are increasingly used to deliver medication adherence interventions, however there is limited evidence of the effect of these interventions on OC adherence. This study aimed to explore the proof-of-concept of a smartphone self-management program to support adherence to oral chemotherapy in young people and adults with cancer. This was a 10-week, non-randomized, multi-site trial. The main outcomes were acceptability and satisfaction with the intervention. The program consisted of SMS-based reminders to take OC, information about OC, and management of adverse effects. Twenty-two participants (17-74 y/o, median age 60 y/o) were recruited at six hospitals with 21 completing post-intervention assessment measures. The sample included 10 different cancer diagnoses (predominance of breast cancer) and 11 OC medications, mostly taken as a single dose (66.7%) continuously (33.3%) or as a 14 day out of 21 day cycle (33.3%). Ninety-five percent of enrolled participants completed post-intervention measures and 81% of the sample reported high satisfaction with the program. The intervention was found to have no effect on supporting adherence to oral chemotherapy (assessed by self-report and medication event monitoring system) in this sample. An increase in knowledge about OC was observed at post-intervention ($p=0.010$). This study demonstrated proof-of-concept of the smartphone self-management program and highlighted the need for intervention and trial design-related refinements before commencing a randomized controlled trial of the intervention.

Keywords: cancer, oral chemotherapy, adherence, self-management, smartphone

1. INTRODUCTION AND BACKGROUND

Oral chemotherapy (OC) drugs offer the advantage of at-home self-administration and are favoured by most patients due to their convenience and acceptability, compared to parenteral

medicines that may require a patient to spend more time at hospital to facilitate administration (Bedell, 2003; Tadic, Spasojevic, Tomasevic, & Dejanovic, 2015). However, OC treatment also encompasses challenges due to the limited hospital supervision and the lack of standard processes for monitoring adherence (taking the medicine as prescribed) and side-effects (Weingart et al., 2008). Many OC-related adverse effects are similar to those observed in parenteral cancer medicines (Hartmann, Haap, Kopp, & Lipp, 2009), but in the former, delays in symptom management and potential for medication errors (e.g. over and under dosage) can lead to poor clinical outcomes, toxicity and health complications, including premature death (Goodin, 2007; Marin et al., 2010; McCowan, Wang, Thompson, Makubate, & Petrie, 2013). Adherence is defined as "the extent to which a persons' medication-taking behavior corresponds with the agreed recommendations of the clinician" (Sabaté, 2003). In adults, non-adherence rates to OC can be as high as 54% (Greer et al., 2016) and there is evidence of these non-adherence rates increasing over time of treatment (Makubate, Donnan, Dewar, Thompson, & McCowan, 2013; Muluneh et al., 2018). Due to their unique developmental stages, adolescents and young adults (AYAs) seem to be at a higher risk of medication non-adherence than children and adults. Whilst evidence on the extent to which AYAs adhere to their OC prescriptions is limited, a small number of studies have found non-adherence rates to OC of between 25% and 53% in this population (Ganesan et al., 2011; Lau, Matsui, Greenberg, & Koren, 1998; Pai, Drotar, & Kodish, 2008; Unnikrishnan et al., 2016; Wu et al., 2018).

The reasons patients fail to take their OC as prescribed can be attributed to multiple factors related to the individual, the healthcare team and system, socio-economic variables, the condition and the therapy (Sabaté, 2003). Therapy-related adverse effects, forgetfulness, and poor knowledge about OC have been identified in the literature as the main modifiable reasons for OC non-adherence (Skrabal Ross, Gunn, Suppiah, Patterson, & Olver 2020). Interventions based on multiple strategies to address OC-related adverse effects and

knowledge seem to be effective in improving adherence to OC (non-endocrine) (Gebbia et al., 2013; Krolop et al., 2013; Lam & Cheung, 2016; Santoleri, Lasala, Logreco, Ranucci, & Costantini, 2019; Simons et al., 2011; Todo et al., 2019).

In chronic diseases in general, short message service (SMS) medication reminders have been shown to improve medication adherence (Hamine, Gerth-Guyette, Faulx, Green, & Ginsburg, 2015; Thakkar et al., 2016). The use of SMS in health-related research has increased in recent years and it is the most common mobile health (mHealth) platform in medication adherence interventions (Hamine et al., 2015) due to 3.5 billion people around the world now using smartphones (Statista, 2020).

Mobile phone-based adherence-enhancing interventions are highly acceptable to their users but little is known about their efficacy in improving adherence to OC (Skrabal Ross, Gunn, Patterson, & Olver, 2018).

The purpose of this study is to explore the proof-of-concept of a novel smartphone self-management intervention that aims to support adherence to OC in AYAs and adults with cancer. The design of the program, detailed elsewhere (Skrabal Ross, Gunn, Patterson, & Olver, 2019), was informed by evidence, a formative study with individuals taking OC, oncology and haematology healthcare professionals, and theoretical and methodological frameworks for the design of mHealth interventions.

2. METHODS

2.1. Study design

This was a multi-site, 10-week, non-randomized, proof-of-concept trial.

2.2. Participants

The trial was approved by many Human Research Ethics Committees. Twenty-two participants were recruited at six public and private hospitals. Recruitment took place between April 2019 and January 2020. Individuals were eligible if they: a) were aged 16 to 75 years, b) were undergoing active or maintenance treatment with oral chemotherapy (cytotoxic and targeted

agents) (Appendix G shows the approved list of OC drugs), c) owned a smartphone, d) had internet access at least once a week, e) were willing to receive and read SMS from the research team, f) had a planned treatment duration with oral chemotherapy and estimated life expectancy of at least 3 months from the beginning of the study, and g) were able to read and speak English. Those participating in other studies aiming to improve oral chemotherapy adherence, as well as those with a self-reported or suspected presence of a condition affecting cognitive functioning (i.e. dementia, psychosis) were excluded.

Participants who completed the study were provided with an A$50 voucher as partial compensation for their time.

2.3. Procedure

Potential participants were identified by cancer services healthcare staff (oncologists, haematologists, nurses, pharmacists) and were referred to the cancer services trial coordinator or investigators to consider participation in the study and complete the enrolment process. Participants received written information about the study and completed a consent form. Individuals 16-17 years old were considered mature enough to provide study consent with no need for parental permission but were encouraged to discuss their participation with their parents or relevant people in their lives before granting consent.

The researcher (XS) or an oncology or haematology clinical trial nurse, conducted baseline assessment measures, face-to-face or over the phone (estimated time 15-20 minutes), before beginning the intervention (week 1). All participants were provided with a child-proof Medication Events Monitoring System (MEMS) device to store and take their OC from for 10 weeks. The device was dispensed and labelled by cancer services pharmacists at the recruitment sites. Pharmacists were provided with verbal and printed information about how to handle and refill MEMS devices (Appendix H contains the document with this information). At the first MEMS OC refill, a researcher (XS) or a cancer services pharmacist provided participants with verbal and printed instructions about the appropriate use of the

MEMS device (see Appendix I shows the instructions for participants). Participants were instructed to start using the device to take their first due OC dose after MEMS collection and to take the MEMS each time a further supply of the OC was prescribed for the duration of the study.

At the end of the study (week 10), post-intervention assessment measures were completed. Appendix J contains the assessment tools used in the study. The study processes are illustrated in Figure 2.

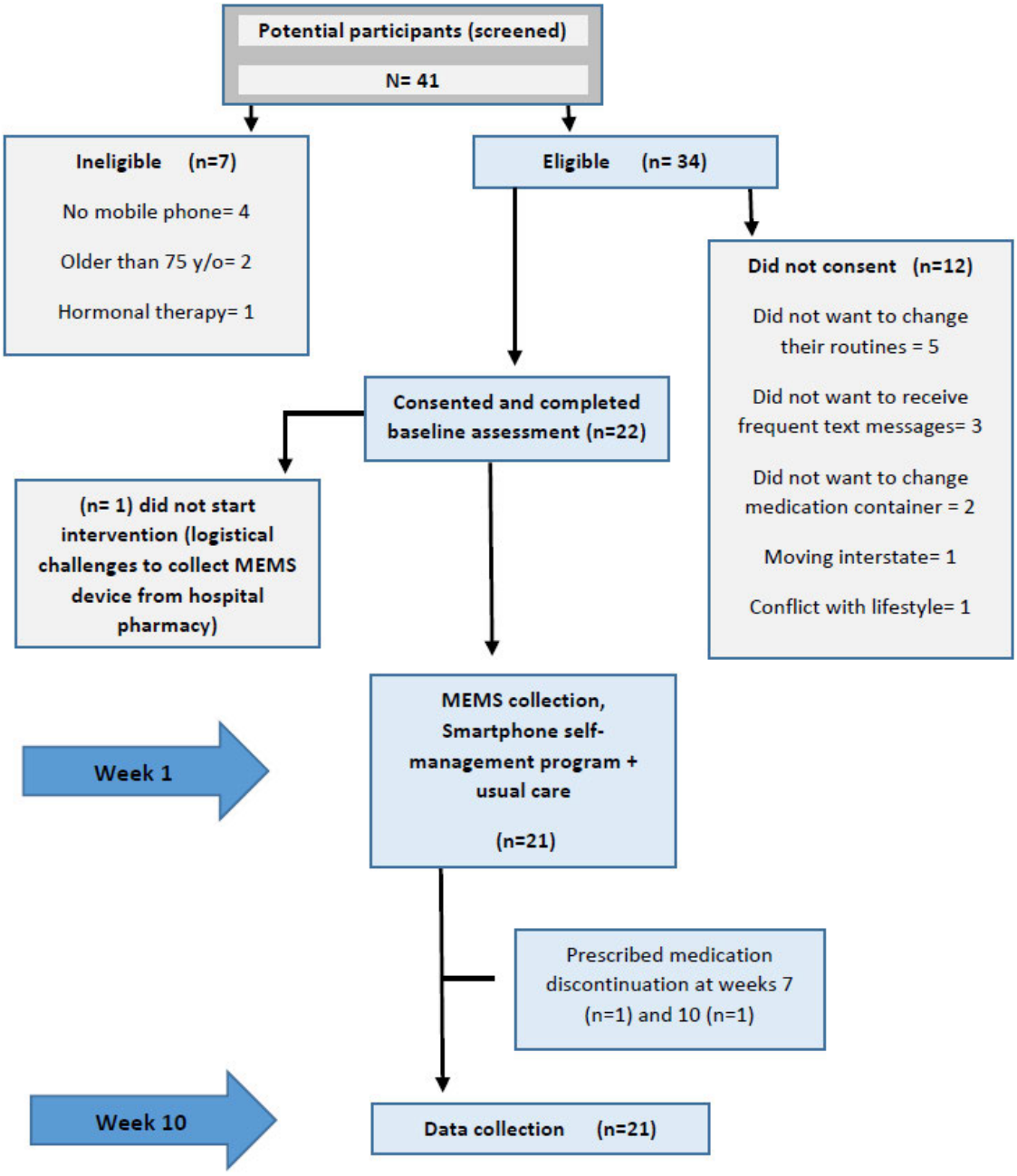
2.4. Outcomes

The main outcomes in this study were the acceptability of and satisfaction with the intervention. Acceptability was defined as the proportion of participants who completed the study out of the number of participants who consented. This encompasses three levels of acceptability: a) high (≥80%), b) moderate (70%-79%), and c) low (≤ 69%). Satisfaction with the intervention was assessed at post-intervention through a short questionnaire used in previous studies (Decker et al., 2009) with acceptable reliability (α>0.65). This questionnaire consisted of 12 items related to intervention satisfaction. Two items assessing participants' satisfaction with the MEMS device as part of the intervention were added to the end of the questionnaire in this study. Scores ranged from 14 to 42 points and were categorized as low satisfaction (14-24), moderate satisfaction (25-33), and high satisfaction (34-42). In this study, high satisfaction with the intervention was defined as ≥75% of the sample with questionnaire scores between 34 and 42 points.

Socio-demographic (e.g. age, education level, marital status) and cancer-related information (i.e. diagnosis, date of diagnosis, name of prescribed OC drug, dose, and schedule), were gathered through a short questionnaire. The instrument also asked about participants' preferred frequency of information about OC and side-effects, which were components of the intervention.

Figure 2

Schematic of study process



Secondary outcomes (knowledge about oral chemotherapy, symptom presence and severity, and self-reported adherence to oral chemotherapy) were assessed at baseline and week 10. Knowledge about oral chemotherapy was measured through a 10-item questionnaire, based on MOATT (Boucher, Lucca, Hooper, Pedulla, & Berry, 2015). Each correct answer equals 1 point adding up to scores ranging between 0-5 (low knowledge), 6-8 (moderate knowledge),

and 9-10 (high knowledge).

Symptom presence and severity were self-assessed through a scale (0-5), where "0" is no symptom and "5" is a severe symptom. These types of Likert scales have been used by previous studies with OC users (Given et al., 2008; Kim et al., 2018; Sherwood et al., 2005). The instrument gathered patient reported information about the presence and severity of 17 main OC-related side-effects: diarrhoea, nausea, fatigue, cough, constipation, weakness, lack of appetite, fever, pain, hand-foot syndrome, mouth sores, dry mouth, numbness and tingling, skin rash/sores, shortness of breath, taste changes, and disturbed sleep.

Self-reporting of oral chemotherapy adherence was assessed through the MARS-5 (Horne, Hankins, & Jenkins, 2001). This five-item, self-report scale assesses intentional and non-intentional non-adherent behaviors such as consciously stopping medications and forgetting to take them. Cronbach's alpha of this scale was found to be 0.68 with a sample of breast cancer patients treated with oral endocrine therapy (tamoxifen) (Grunfeld, Hunter, Sikka, & Mittal, 2005). In MARS-5 adherence is frequently defined as a score of 25, which is the maximum score. There is evidence that under this score MARS-5 is not able to reach enough sensitivity and specificity to detect non-adherence to medication (Tommelein, Mehuys, Van Tongelen, Brusselle, & Boussery, 2014). In this study MARS-5 scores ranged 0 to 5, with a dichotomized measure of adherence (adherent=0 points and non-adherent $\geq$ 0 points).

Another measure of adherence to oral chemotherapy used in this study was the MEMS device (AARDEX Group), which was used from weeks 1 to 10. The device consists of a bottle to store medication and an electronic, child-resistant cap that tracked the frequency and time of openings (counted as medication-taking events). Participants were considered to be adherent to OC if 80% or more of the prescribed OC doses were taken during the 10 weeks of study. This is the most commonly used adherence threshold employed in medication adherence studies, including OC (Nguyen, La Caze, & Cottrell, 2014).

2.5. Intervention

The self-management program was provided to all study participants in addition to usual cancer care for 10 weeks. It was delivered exclusively via SMS which were sent via an online text message gateway with automation solutions. SMS reminders to take OC consisted of a one-way (no need to reply) short message which showed the name of the participant and the text "*please take your oral cancer medication now. If you need further support, let us know and we will be happy to help (name and phone hospital contact)*". These messages were delivered 15 minutes before each OC dose was due and tailored to the individual's medication schedule. End of the study SMS were sent on the last day of week 10. Participants, treating medical oncologists or haematologists and nurses, as well as cancer services pharmacists were all instructed to report changes in participants' OC schedule to the researcher XSR (e.g. dose or medication changes, withholding of medicine, also known as drug holidays) to avoid delivering medication reminders when they were not required.

Information about OC and information about management of side-effects were both delivered via SMS hyperlinks to Portable Document Format (PDF) online documents, securely stored in Google Drive. This information was delivered at the frequency (weekly, fortnightly, monthly, or all at the beginning) chosen by each participant at baseline.

The strategy "information about oral chemotherapy" consisted of five individual documents, following the MOATT (Rittenberg, 2012). Individual documents on how to manage the main five adverse effects from each OC in the study (as per the product information) were designed based on the Symptom Management Toolkit (Given, Given, & Majeske, 2014), with permission from the Michigan State University (Appendix K shows the Agreement with the Michigan State University). The language in the Toolkit was adapted to suit the Australian context by an experienced medical oncologist (IO). Appendix L provides an example of the information about OC and information about side-effects provided to study participants treated with Dasatinib.

2.6. Statistical Methods

Descriptive statistics (i.e. frequencies, measures of central tendency, variability) were used to analyze the outcome and demographic variables. Acceptability of the intervention was reported as the percentage of the number of participants who completed the study out of the number of participants who consented to the study. The proportion of participants who enrolled in the study out of the number of eligible participants was also described, with reasons for rejection and exclusion provided. This method has been used in previous studies (Spoelstra et al., 2016; von Hammerstein et al., 2019).

Pre and post-intervention comparisons for secondary outcomes were performed using chi-square tests for categorical outcomes or t-tests for continuous outcomes. Daily individual adherence to OC was registered by assigning a "1" when the actual MEMS opening corresponded with the number of expected MEMS openings (according to individual OC prescriptions) and a "0" was assigned when this condition wasn't met. Then, individual weekly rates of adherence were obtained by calculating the average of daily adherence scores for each week and converting to percentages. Weekly adherence rates for the study cohort were calculated by computing average rates for each week (1 to 10). These averages included only participants who were active in the study each week, when adherence data was available and not censored due to prescribed medication discontinuation or lack of available data.

Analysis of variance (ANOVA) was used to explore differences between age groups (16-25, 26-50, 51-60, and 61-75 years old) in the satisfaction questionnaire. SPSS version 26 (IBM Corp., Armonk NY, USA) was used for all analyses. The comments section in the satisfaction questionnaire provided a descriptive insight into participants' satisfaction and challenges with the program and its components. Data were analysed using Thematic Analysis (Braun & Clarke, 2006) and common themes were reported.

3. RESULTS

3.1. Study participants

Twenty-one participants took part in the study. Participant median age was 60 y/o (range 17-74 y/o) and most of them were older than 50 y/o (66.7%). There was a slight predominance of females (52.4%) and the majority were married (76.2%). A diversity of cancer diagnoses were observed (10) with the most common being breast cancer (33.3%). Several OC drugs (11) were included. There was a good spread of times since cancer diagnoses in the sample (median=28 months, range= 1-163 months). The majority had a single dose prescription (66.7%) and either took the medication on a continuous basis (33.3%) or in cycles of two weeks on and one week off the medicine (33.3%). Demographic and cancer-related information for the sample is described in Table 1.

TABLE 1

Sample baseline demographic and cancer–related characteristics

Characteristics	N=21 (n)	%
Gender		
Female	11	52.4
Male	10	47.6
Age (years) Median=60, Range= 17-74		
16-25	3	14.3
26-50	4	19.0
51-75	14	66.7
Marital status		
Married	16	76.2
Separated	1	4.8
Widowed	1	4.8
Never married	3	14.2
Education level		
Finished primary school	4	19.1
Finished high school	8	38.1
Trade certificate	5	23.8
University degree/diploma	2	9.5
Post-graduate degree/diploma	2	9.5
Employment status		

Full-time	4	19.0
Part-time	2	9.5
Casual	1	4.8
Not employed, not looking for a job	5	23.8
Not employed, looking for a job	1	4.8
Retired	8	38.1
Cancer diagnosis		
Colon	1	4.8
Bladder	1	4.8
Lung	2	9.5
Breast	7	33.3
Brain	2	9.5
Blood cancers	3	14.3
Gastric	2	9.5
Oesophagus	1	4.8
Pancreatic	1	4.8
Connective tissue	1	4.8
Drug name		
Capecitabine	6	28.6
Palbociclib	3	14.3
Ribociclib	2	9.5
Temozolomide	2	9.5
Dasatinib	2	9.5
Erlotinib	1	4.8
Osimertinib	1	4.8
Nilotinib	1	4.8
Sunitinib	1	4.8
Hydroxyurea	1	4.8
Neratinib	1	4.8
Time since diagnosis (months) (Median=28, Range= 1-163)		
0-6	5	23.8
7-12	3	14.3
13-24	2	9.5
25-59	6	28.6
60 +	5	23.8
Prescribed drug frequency		
Once a day	14	66.7
Twice a day	7	33.3
Cycle length		
2 weeks on- 1 week off	7	33.3
3 weeks on- 1 week off	5	23.8
5 days on- 23 days off	2	9.5

Continuous	7	33.3

3.2. Participants' Acceptability and Satisfaction

In total, 41 potential participants were approached at six recruitment hospitals, seven of them did not meet the inclusion criteria and 12 did not consent to the study. The main reasons for not consenting were unwillingness to change their routines (5/12) or to receive frequent SMS (3/12). Figure 2 shows the reasons for exclusion and rejection of enrolment into the study. Twenty-two out of 34 (64%) of the eligible patients approached enrolled in the study. However, one of them lived in a rural area and could not collect the MEMS device from the hospital pharmacy, which made the participant ineligible to begin the intervention.

Acceptability of the intervention was found to be high, 95% (21/22) of the enrolled participants remained in the study and completed post-intervention assessment tools. 2/21 participants had their OC medication discontinued by their medical oncologist before the end of the study (day 43, week 7, and day 64, week 10). However, this did not compromise participants' acceptability of the program as the decision was made by the medical oncologist.

A total of 1,686 SMS texts were sent to participants. Out of this number, only 16 SMS (0.9%) failed to reach the intended recipients' smartphones. Eleven out of these 16 SMS were reminders to take OC and the rest contained a hyperlink to information about oral chemotherapy or management of side-effects. The cost to deliver the SMS to 21 participants for 10 weeks was AUD $0.082 per SMS (total AUD $124.26).

Eighty one percent of the sample (17/21) reported high satisfaction with the intervention (questionnaire scores range= 34-42) and satisfaction was moderate (questionnaire scores range 25-33) for the remaining participants (4/21, 19%).

No significant differences in satisfaction scores were found between females and males (p= 0.689; Appendix M) or between age groups (p= 0.860; Appendix M)

The analysis of participants' responses to individual questionnaire items allowed exploration of satisfaction with each component of the program. Table 2 shows the sample's answers in

the satisfaction questionnaire and Appendix N offers this information by age group and gender.

TABLE 2

Responses to the items in the satisfaction questionnaire (N=21)

Item	n	%
1. How satisfied are you overall with your participation in the study?		
Not at all	0	0
Somewhat	2	9.5
Very much	8	38.1
Highly	11	52.4
2. Did you have any problems with the text message system?		
Yes	0	0
No	21	100
3. Did you have any problems accessing the information about oral cancer medication and symptom management?		
Yes	1	4.8
No	20	95.2
4. Overall, for you personally, the text messaging was		
Mostly helpful	18	85.7
Neutral	2	9.5
Not helpful	1	4.8
5. The information about your oral cancer medication and symptom management was		
Very helpful	10	47.6
Helpful	8	38.1
Somewhat helpful	3	14.3
Not helpful	0	0
6. Did the text messages help you take your cancer medication on time?		
Helped	17	81
Neutral	3	14.3
Did not help	1	4.7
7. How satisfied were you with text reminders to take your medications?		
Not at all	0	0
Somewhat	4	19.0
Very much	7	33.3
Highly	10	47.6
8. How satisfied were you with the information about your oral cancer medication and symptom management?		
Not at all	1	4.8
Somewhat	3	14.3
Very much	7	33.3
Highly	10	47.6
9. Did you read the text message medication reminders?		
All of the time	7	33.3
Most of the time	11	52.4
Some of the time	3	14.3
None of the time	0	0
10. Did you read the information about your oral cancer medication and symptom management?		

All of the time	7	33.3
Most of the time	7	33.3
Some of the time	6	28.6
None of the time	1	4.8
11. Would you recommend text messages as a reminder to take your cancer medication?		
Yes	21	100
No	0	0
12. Would you recommend the smartphone program (text messages and information) to other people who have been prescribed cancer medication?		
Yes	21	100
No	0	0
13. Did you use the medication container provided in the study during all 10 weeks?		
Yes	21	100
No	0	0
14. Did you find any challenges in using the medication container?		
Yes	4	19.0
No	17	81

Regarding satisfaction with the overall intervention (items 1 and 12), all of the participants would recommend the program (reminders, information about oral chemotherapy, and management of side-effects) to other people who are prescribed OC. Most participants expressed high (52.4%) and very high (38.1%) satisfaction with their participation in the study.

Qualitative comments provided insights into particular elements of the program that were valued.

> "Helpful program for people who struggle to remember. It gives you enthusiasm to continue to take it" (P13)
>
> "It was a very helpful program. Living in the country we have bad reception, a few times messages were delayed, not too bad a little bit. It worked pretty good actually" (P9)

In terms of SMS reminders (items 2, 4, 6, 7, 9, 11), none of the participants reported problems with the text message system and all of them said they would recommend SMS as reminders to take OC. Most participants (80.1%) were highly/very much satisfied with SMS reminders, which were evaluated by participants as being mostly helpful (85.7%). Three out of seven

(42.9%) participants aged 61-75 were “somewhat satisfied” with the SMS reminders but most of them (6/7, 85.7%) rated the SMS as being mostly helpful. The SMS served to remind most OC users (81%) to take their medicines on time and were read all of the time (33.3%) and most of the time (52.4%).

In the qualitative section of the questionnaire participants expressed that SMS helped them to take their OC.

> “I am missing the SMS now that I am not receiving them. It was quite good because if I didn't take it on time I felt guilty and took it” (P15)

Despite no issues with SMS reminders being reported in the multiple selection items of the questionnaire, data from the comments section allowed identification of delays in receiving SMS for three participants who lived out of the metropolitan areas, where mobile phone coverage tends to be unstable.

> “Phone reception in the country is bad so sometimes I got SMS about oral chemotherapy and side effects as late as 2 am” (P6)
>
> “Sometimes I got the messages 15 minutes before medication was due and sometimes I didn't. We live in the country” (P16)

The information about OC and management of side-effects component of the program (items 3,5,8,10) was deemed by most participants to be very helpful (47.6%) or helpful (38.1%). Although a high percentage of the sample (81%) was highly/very much satisfied with these components of the program, lower satisfaction was found in 4/21 of participants (19%). Only 66.7% read the information always or most of the time. 50% (5/10) of males read this information some or none of the time. Some participants stated that they already knew about this information and they did not find a need to read it or it reminded them of their disease, as it was expressed in the qualitative section of the questionnaire.

> “I already knew information about oral chemotherapy from nurses at the hospital. I only read one of these messages and decided not to read the rest because it was a

reminder that I was sick" (P6)

"I'd already started the chemo… a lot of the info was redundant. If I hadn't started and I was new with the med that would be different" (P12)

MEMS devices (items 13, 14) were used during the 10 weeks of the study by all participants and a small number of them (4/21, 19%) reported having issues with the device. These issues were related to difficulties taking the medications out of the bottles or participants' perception that the device was not working because they expected to hear a sound when opening, which did not happen all the time.

"When the bottle was full it was hard to take medication out" P7

"Often didn't work, it didn't click and I think that means that didn't record the drug taking" P16

3.3. Adherence to oral chemotherapy

Most participants reported being adherent to their OC at baseline (16/21, 76%) and post-intervention (17/21, 81%; p= 0.707).

Adherence to OC assessed through MEMS was analyzed for 19/21 of the participants, due to unavailability and censoring of two MEMS devices.

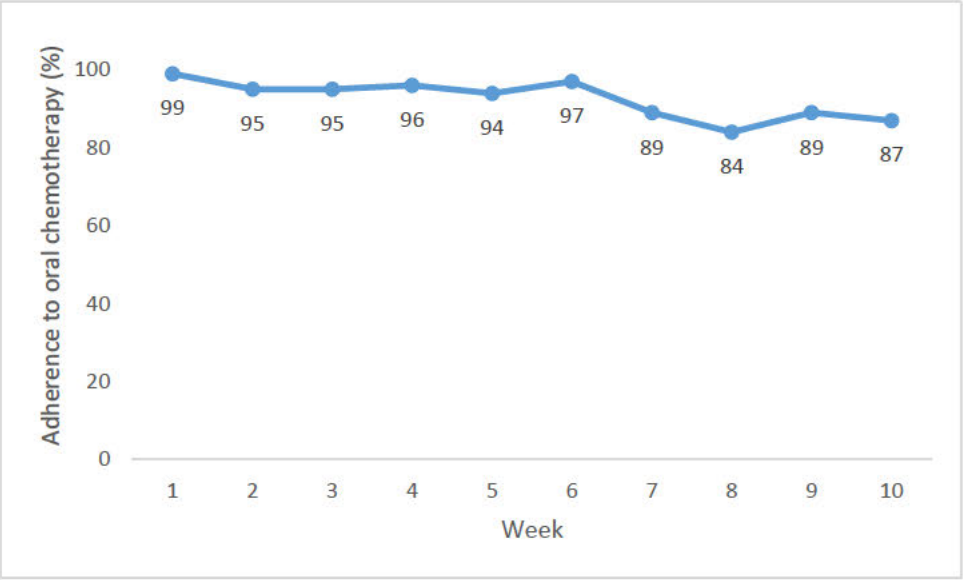
Most participants (17/19, 89.5%) were adherent to OC during the study (individual summed adherence scores week 1-week 10). Appendix O shows participants' weekly adherence rates. Twelve out of these 17 participants (63.2%) were adherent to OC at all weeks of the study. However, 3/19 (15.7%) participants were consistently non-adherent from week 7 until the end of the study (adherence rates range= 14%-71%). All of these non-adherers were younger patients (23-31 y/o) and took their medications (targeted therapy) on a continuous basis (no cycles). An additional 4/19 (21%) participants had 1 to 3 non-consecutive weeks of non-adherence, most of them had a breast cancer diagnosis and took the OC in cycles (2 weeks on, 1 week off, and 3 weeks on, 1 week off).

The overall sample's adherence rates for each of the weeks was higher than 80% (range= 84-

99%), with the lowest found at week 8 (84%) and the highest at week 1 (99%). A trend towards a decrease in adherence rates for the study population was observed from week 7. Figure 3 shows the sample's rates of adherence from week 1 to 10.

Figure 3

Participants' weekly rates of adherence to oral chemotherapy N=19 (measured by Medication Event Monitoring System)



3.4. Knowledge about oral chemotherapy

A paired-samples t-test showed a significant difference between participants' scores in knowledge about oral chemotherapy at baseline (M=7.57, SD=1.502) and post-intervention (M=8.48, SD=1.209; p= 0.010). These results suggest that the intervention increased knowledge about oral chemotherapy after 10 weeks of participation in the self-management program.

The number of participants with high knowledge about OC (questionnaire scores range= 9-10) increased from baseline (n=5) to post-intervention (n=14). Additionally, a reduction in the number of participants with low levels of knowledge about oral chemotherapy (scores range=0-5, n=0) and moderate levels (scores range=6-8, n=7) was observed at post-intervention (week 10). Table 3 shows descriptive statistics for the sample across levels of knowledge before and after the intervention.

TABLE 3

Distribution of the sample across levels of knowledge about chemotherapy before and after the intervention

	Baseline (N=21)	Post-intervention (N=21)
Low knowledge scores (n)[a]	3	0
Moderate knowledge scores (n)[b]	13	7
High knowledge scores (n)[c]	5	14
Mean	7.57	8.48
Standard deviation	1.50	1.20
P= 0.010		

[a]Low knowledge scores range (0-5), [b] moderate knowledge scores range (6-8), [c] high knowledge scores range (9-10)

3.5. Symptom presence and severity

A number of symptoms were identified in this sample of OC users. In this study, for analysis purposes, "symptom presence" refers only to those symptoms for which severity scores ≥3 (moderate-severe) in the symptom scale were reported.

Paired samples t-tests showed that there were no significant differences between baseline and post-intervention assessment for the presence of symptoms (M= 3.10, SD=2.79 and M=4.43, SD=2.97 respectively; p=0.087) and symptom severity (M = 16.19, SD=11.81 and M=20.43, SD=12.06 respectively; p=0.155). A non-significant increase in both symptom presence and symptom severity scores were observed from baseline to post-intervention (N=21).

Of the 17 symptoms assessed, those most frequently reported with severity scores ≥3 (moderate-severe) at baseline and week 10 were fatigue (n= 9 and 15 respectively), disturbed sleep (n= 9 and 10 respectively) and dry mouth (n= 6 and 9 respectively). These symptoms were also found to be the most severe (summed severity scores: fatigue 42 and 55 respectively, disturbed sleep 41 and 41 respectively, and dry mouth 27 and 34 respectively). Although weakness was not amongst the most frequently reported symptoms, it was one of the most severe at baseline and week 10 (severity summed scores= 30 and 33 respectively). Appendix P shows pre and post-intervention sample scores in symptom presence and severity

scale for each of the 17 symptoms assessed.

4. DISCUSSION

This study demonstrated proof-of-concept of a smartphone self-management program to support adherence to OC. Acceptability of and satisfaction with the intervention was high, with 95% of the enrolled participants completing post-intervention measures and 81% of the participants reporting high satisfaction with the program.

High satisfaction with the intervention was observed across all components of the program (SMS reminders, information about oral chemotherapy, and management of adverse effects). However, only half of the males reported reading the information about OC and adverse effects some or none of the time. The researchers are not aware of evidence on ways for mobile phone-based information delivery that may specifically improve men's engagement with these aspects of the intervention. It may be useful for future studies to explore gender-based use of different information strategies (e.g. on-demand coaching, motivational interviewing or chatbots to educate about OC) in mobile phone-based interventions to support adherence to OC.

Issues with the timing of the SMS (reminders not received 15 minutes before the due OC dose, information received late at night) were reported by participants living outside of metropolitan areas, where mobile reception tends to be unstable. Failure of rurally based participants to receive 40% of SMS, as part of an OC adherence intervention, was reported by a previous Australian study (Pereira-Salgado et al., 2017) and this issue should be taken into consideration when designing future mobile phone-based trials. In these settings, apps or Multimedia Messaging Service (MMS) delivered by Wi-Fi may have greater reach.

The automated text message online platform in this study only failed to deliver 0.9% of the 1686 scheduled SMS, most of them were reminders to take OC. This shows that SMS platforms can be highly reliable to deliver reminders to take medication. The SMS online platform in this study is a cost-effective method that allowed delivery of not only short

messages with medication reminders, but also larger contents of information through SMS hyperlinks at a total cost of AUD $124.26 for 21 people over a 10-week period, plus the time of the researcher to input the relevant information in to the program .

Self-reported adherence to OC was mostly consistent at baseline and post-intervention, with most participants being adherent at baseline and 1/5 of the non-adherent participants reporting to be adherent to OC at post-intervention. When data from MEMS were analyzed and averaged for the 10 weeks of study, ≥ 80% adherence was observed across all weeks. However, a tendency towards a decrease in these rates was evident after week 7. The present trial did not assign a baseline period for the use of MEMS which may have caused a Hawthorne effect on participants' adherence behavior. Previous evidence has established a relationship between the use of MEMS and initial higher measures of medication adherence which stabilized after up to 40 days in people diagnosed with HIV (Deschamps, Wijngaerden, Denhaerynck, Geest, & Vandamme, 2006) and diabetes (Sutton et al., 2014). However, there was no evidence of a Hawthorne effect on medication adherence in people with schizophrenia who used MEMS for 3 months (Acosta et al., 2013). Future trials need to consider the early introduction of MEMS devices in the studies (approximately 40 days before intervention delivery) to minimize the possible MEMS influence on adherence behavior.

The smartphone self-management program increased OC knowledge at post-intervention and more than doubled the number of people within the higher ranges of knowledge after 10 weeks. A future randomized controlled trial of the intervention would be useful to identify if there are significant differences between people who participate in the program and those under standard cancer care.

An increase in the report of both symptom presence and severity were observed at post-intervention. It is possible that the smartphone self-management program did not improve symptoms in this cohort but it is also likely that participants felt more comfortable in reporting their symptoms after 10 weeks of intervention, especially considering that the

information provided contained advice on how to report symptoms. A previous study which used the printed version of the Symptom Management Toolkit found higher symptom severity in participants who used the Toolkit compared to those who did not (Spoelstra et al., 2015). Future trials may benefit from utilizing methods to increase the confidence of study participants with reporting symptoms at baseline.

4.1. Limitations

Although the sample numbers in this study were deemed to be sufficient to allow examination of a proof-of-concept of the intervention, it was not powered to detect differences between sub-groups in the primary outcomes or sample differences in secondary outcomes. Our findings on adherence to OC, knowledge about oral chemotherapy and symptom presence and severity should be treated as preliminary and not generalizable, as they were conducted with a small sample, to evaluate the need for future refinements of the intervention used in this study. Additionally, due to the lack of a comparison group, it is not possible to know whether the intervention group would have shown better adherence to OC or knowledge than patients receiving standard care. The fact that most participants were adherent at baseline, as was the case in this study, has been considered by previous research as a possible reason for the lack of significant effects of mobile phone-based interventions on adherence to OC (Greer et al., 2020; Spoelstra et al., 2015). The use of a heterogeneous sample, with a variety of cancer diagnoses and OC therapies, may also have affected findings on adherence to OC in this study. Future randomized controlled trials of interventions should purposively sample OC users who present as non-adherent to OC at baseline and reduce the sample's treatment-related differences by including those diagnosed with one cancer type and treated with the same OC. Even though it may be ideal to have a study population as homogeneous as possible with the criteria listed above, it is also important to consider that it took nine months across six sites to recruit participants for this study without these stringent criteria.

This smartphone-based intervention to support adherence to OC showed high acceptability

and satisfaction amongst AYA and adult OC users. However, carefully thought out intervention refinements are needed before conducting a larger randomized controlled trial.

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CHAPTER VII. Conclusions, Limitations, and Recommendations

7.1. Conclusions

The purpose of this research was to examine proof-of-concept of a smartphone self-management intervention to support adherence to OC in AYAs and adult cancer patients. In doing so, two key research questions were posed:

What are the levels of acceptability of a smartphone self-management program to support adherence to OC?

What are the levels of satisfaction with a smartphone self-management program to support adherence to OC?

We anticipated that the program (designed upon patients' input, careful examination of evidence on the reasons for OC non-adherence and strategies to improve these reasons, and theoretical and methodological frameworks) would have high acceptability and satisfaction amongst OC users.

To address these questions, there were five objectives of this research. To:

1) Conduct an extensive literature review to identify the main reasons for OC non-adherence and explore the impact, available interventions and assessment methods for these factors.

2) Determine the preferences of AYA and adult cancer patients on the structure and features of a smartphone self-management program that aims to support adherence to OC.

3) Conduct a scoping review to explore what was known about available mobile phone-based interventions to support OC adherence, their utility in increasing OC adherence, and to identify opportunities for future research.

4) Design a smartphone self-management program to support adherence to OC in AYA and adults with cancer based on end-users' preferences, healthcare professionals' recommendations and evidence-based strategies.

5) Explore proof-of-concept of the smartphone self-management program with AYA

and adults with cancer.

Four papers containing important findings were produced during the candidature. When placed together, these papers complemented by evidence described in this thesis, demonstrate that the research objectives were met, leading to the successful development and trial of a novel smartphone self-management program to support OC adherence in AYAs and adults with cancer.

This research offers a new approach to address the issue of non-adherence to OC in young and adults with cancer. The novel smartphone self-management program was demonstrated to be a cost-effective tool that was highly acceptable to users and has the potential to be implemented into standard oncology care. Although the effectiveness of the program in supporting adherence to OC is yet to be determined by a future RCT, the proof-of-concept study in this thesis offers important information about future intervention and methodological refinements that need to be considered before conducting a larger trial of the intervention.

An initial overview of the literature allowed understanding of the challenges in monitoring OC adherence and side-effects in light of lacking standardized oncology monitoring processes to support OC users. The overview also provided information about high rates of non-adherence to OC in adults and AYAs. This established the need to provide OC users with self-management tools to support their OC adherence. Recent efforts to address this global health issue through mobile phone-based interventions, especially those using SMS, appeared promising in increasing medication adherence in chronic diseases.

In order to design a self-management tool to support OC adherence, it was important to understand the reasons that OC users fail to take their medication as prescribed. In Chapter II, OC-related side-effects, forgetfulness and poor knowledge about OC were identified as the main factors for OC non-adherence.

OC users were engaged in the design of the program. Chapter III described findings

from a qualitative formative study with OC users. This study allowed identification of the components and structure of the smartphone self-management program and positioned SMS as the preferred platform to deliver the program.

The need and relevance for the development and evaluation of an SMS-based tool for AYAs and adults with cancer that integrates strategies to address the three main reasons for OC non-adherence was identified and addressed through the evidence and consumer-informed design of a novel smartphone self-management program. Findings from the proof-of-concept trial of the program highlighted users' high satisfaction and acceptability with the intervention and an increase in knowledge about OC after 10 weeks. Adherence to OC was not improved by the intervention within the sample employed in this study which presented as highly adherent to their OC at baseline. The purposive inclusion of non-adherers to OC and the use of a more homogeneous sample with the same cancer diagnoses and OC treatment are amongst the suggested considerations for a future RCT of the program.

7.2. Limitations and Recommendations

The literature reviews in Papers 1 and 2 were essential to identify the main modifiable factors for non-adherence to OC and knowledge gaps in the provision of adherence-enhancing strategies delivered via mobile phone platforms. However, due to the nature of the reviews, they did not account for studies with weak methodology and assessment bias, as is the case in systematic reviews. This may affect the generalizability of the findings.

In Paper 1, the unavailability of literature reviews with exclusive focus on determinants of OC non-adherence and the low number of research-based studies of this type, led to the inclusion of studies on oral endocrine therapy. The strategies incorporated into the smartphone self-management program in this thesis were based on findings from Paper 1 but it was not possible to determine whether OC users face additional adherence-related challenges than those prescribed with oral endocrine therapy. Additionally, most of the studies reviewed in Paper 1 were conducted with people diagnosed with breast cancer and

CML and there was a lack of evidence on the reasons AYAs fail to adhere to OC prescriptions. However, in section 2.4 of this thesis the main determinants of non-adherence to OAD (that include both OC and oral endocrine therapies) and medication for chronic diseases were found to be in agreement, which suggests these factors may be present across people treated with different medications, including OC. Despite this, there is still a need for more research to investigate the reasons for OC non-adherence in AYAs and adults with cancer diagnoses other than breast and CML.

The formative study described in Chapter III of this thesis had an under-representation of women and despite efforts from the research team to include adolescents in the study, this age group was not represented. However, study findings did not show preferences for features of the smartphone program that were age or gender specific. This study was the first to investigate OC users' preferences about multiple features with potential to be tailored in SMS interventions. Tailoring mHealth intervention's features may increase the effectiveness of the interventions and future research should consider conducting formative studies (similar to the one described in this thesis) to inform the design of their mHealth interventions.

The number of AYA participants in the formative and proof-of-concept studies was lower than expected. While previous studies have consistently reported low recruitment rates of AYAs (Bleyer, Montello, Budd, & Saxman, 2005; Fern et al., 2008; Ferrari et al., 2009; Sansom-Daly et al., 2019), aligning AYA research with five key criteria (available, accessible, aware, appropriate, and acceptable) (Fern, Lewandowski, Coxon, & Whelan, 2014) and investing in full-time on-site research personnel (and training) (Rosenberg et al., 2019; Sansom-Daly et al., 2019) may be promising strategies to improve participation of AYAs with cancer in clinical trials. The main challenge faced in our studies was the lack of potential participants in the two sites (one for adolescents and one for young adults) in South Australia. Investment in hospital-based research staff and collaboration with a higher number of AYA treating hospitals may help to overcome recruitment barriers in future studies.

The complexity of oral medication schedules, that involve taking a high number of drugs to treat cancer and other chronic conditions, was highlighted in the formative study described in Chapter III of this thesis. Considering the similarity between the barriers to medication adherence in chronic diseases and cancer treated with oral chemotherapy (Chapter II), it is recommended that future research contemplate employing a holistic approach to the development and trial of tools to support adherence to concurrent medications. These types of tools may be more practical and beneficial to patients with multiple drug prescriptions than those that only support adherence to oral chemotherapy.

The research in this thesis helps to address the lack of evidence on mobile phone-based interventions to increase adherence to OC. Future trials of mHealth interventions to support OC adherence should carefully consider the use of homogeneous samples (e.g. same cancer diagnose and OC medication) to reduce undesired variability that may influence the effect of interventions on OC adherence. High satisfaction and acceptability of the smartphone program in this research was found but there is a need for future trials of these types of interventions to consider the purposive inclusion of individuals who present as non-adherent to OC prior to receiving the intervention. This will help to reduce ceiling effect (limitation in measurement of a variable due to high scores being reached)(Salkind, 2010) by providing room for improvement in OC adherence which was lacking in the trial of the smartphone program in this research and previous studies (Greer et al., 2020; Linder et al., 2019; Spoelstra et al., 2016).

Future RCTs of OC adherence-enhancing interventions should also explore the moderator roles of anxiety and length of treatment and the association between perceived ability to manage side-effects and adherence to OC, as the relevance of these variables has been suggested by previous research (Eliasson et al., 2011; Greer et al., 2017; Jiang et al., 2019; Noens et al., 2009; Spoelstra et al., 2016) . Additionally, future research should consider the rurality of users of mobile phone-based interventions, where challenges

associated with mobile phone reception and therefore technology-related issues of delivery cannot be fully overcome.

SMS-based interventions to support adherence to OC are feasible in AYA and adults with cancer. Smartphones are highly available to users worldwide and are an ideal tool to deliver not only short medication reminders but also adherence-enhancing strategies with large amounts of information. Automated SMS platforms are of a low cost and present minimal failures. If found effective in supporting OC adherence, the smartphone program would be highly relevant to oncology settings, especially in less developed countries which are known to be disadvantaged by lower socio-economic and healthcare resources than developed countries.

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Appendices

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Appendix A- Statements of authorship

Statement of Authors' Contribution to Paper 1.

Skrabal Ross, X., Gunn, K. M., Suppiah, V., Patterson, P., & Olver, I. (2020). A Review of Factors Influencing Non-Adherence to Oral Antineoplastic Drugs. *Support Care Cancer*. doi:10.1007/s00520-020-05469-y

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Statement of Authors' Contribution to Paper 3.

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Appendix C- Demographics and selection criteria

Demographics and selection criteria

1. Do you currently suffer from any conditions that affect your judgement (e.g. dementia, psychosis)?
☐Yes ☐No

2. If the answer is Yes, what is the name of the condition?
_____

(if the answer is yes, potential participant will be informed that the presence of such condition is an exclusion criteria for this study)

3. What is your gender? ☐Male ☐Female Other_____

4. What is your age (in whole years from your last birthday)? _____

5. What is your marital status?

☐ Married or living with a partner

☐ Separated/ divorced

☐ Widowed

☐ Never married

6. What is your highest educational qualification you have completed?

☐ Did not finish primary school

☐ Finished primary school

☐ Finished high school

☐ Trade certificate, apprenticeship, diploma or certificate from a college or TAFE

☐ Degree or diploma from a university

☐ Postgraduate degree

7. In which country were you born? _____

8. Do you own a smartphone (a device that combines a cell phone with a handheld computer, typically offering Internet access, data storage, email capability, etc)? ☐Yes ☐No

9. Do you use your smartphone to send/receive text messages? ☐Yes ☐No

10. Do you receive/send messages through apps? E.g. whatsapp, wechat, etc ? ☐Yes ☐No

11. In the last 4 weeks how often did you send/receive text messages?

☐ Less than once a week

☐ Once a week

☐ Once a day

☐ Several times a day

12. Are you currently taking prescribed cancer tablets? ☐Yes ☐No

13. If the answer is Yes, when did you start taking cancer tablets? _____

14. If the answer is No, when did you finish taking cancer tablets?
_____

15. Are you currently taking part in any research that is focused on helping you to improve the way you take your cancer tablets? ☐Yes ☐No

Appendix D- Interview script

Interview Script

Greetings

Remind the interview will be recorded

Remind participation is voluntary

Ask to let me know if feeling uncomfortable or distressed at any time during the interview and need to take a break or would like to stop and try again another day.

Explain the 2 parts of the interview

Any questions?

DEMOGRAPHIC QUESTIONNAIRE---------COMPLETE

Keep in mind that during the interview we are interested in listening to your own individual experiences and preferences.

Imagine that you receive text messages on your phone reminding you to take your cancer tablets.

Section 1

Topic A) Text message sender

Is it relevant to you who is sending the reminder message? Can you tell me a little bit more about it?

Prompt (Who would you prefer to send you the messages?)

Tell me what it would be like if it was someone outside the hospital team e.g. myself or another researcher sent you the message?

Topic B) Format of text message

As you know, messages can be received on smartphones through different apps (conventional text messages, whatsapp, wechat, etc). For messages reminding you to take the cancer tablets. Is there any app that you would prefer? Why?

Smartphone messages can contain text, videos, photos, etc. How would you like the reminder message to be?

For cancer tablets reminder messages, Would you prefer to receive messages only or also respond to the person who sends the message?

Topic C) When

When is good time of the day to receive text messages reminding you to take your cancer tablets? Why?

Topic D) Frequency of text messages

How often would you like to receive reminder text messages? Why?

Topic E) Personalization of text messages

Would you like reminder messages that contain any of your personal information (e.g. your name, name of the cancer tablets you take, etc)?

Prompt- if personalization preference (What personal information would you like the messages to show?)

Section 2.

Please select one of the two messages for each situation, according to your preferences. If you don't like the messages please tell me what would be an appropriate message in that situation?

(Ask after each selection why do you like that option?)

Situation	Text Message Content Options
Busy at home	☐ Please take your XXX now. Taking your XXX is easy, even when you are busy. Organize daily breaks at the time of your medication. ☐Time to take your XXX. Are you busy? Take a break to have your medication. You can do it! ☐Your message
No one around to remind you	☐Please take your XXX now. Taking your tablets is easy, use these messages to remember, even when there's no one around to remind you. ☐Please take your XXX now. No one around to remind you? This text message is your reminder. You can do it! ☐Your message (please write)

With family members or in a public place	☐Time to take your XXX. If taking your tablets in front of other people makes you feel uncomfortable, find a private place e.g. a bathroom or an empty room. ☐Please take your XXX now. If you don't feel comfortable taking your tablets in front of other people, find a private space. You can do it! ☐Your message
Leave the house or travel	☐Time to take your XXX. If you plan to be out of the house at the time to take your tablets always take them with you. You can do it! ☐Please take your XXX now. Always remember to take your tablets with you when you leave home. You can do it! ☐Your message
Take cancer tablets more than once a day	☐ Please take your XXX now. Remember to stop and take your tablets as many times it was prescribed by your doctor. You are in control of your treatment! ☐ Time to take XXX. If the tablets are meant to be taken more than once a day please do it. Following prescriptions can help you to achieve better results. ☐Your message
Take cancer tablets and other medicines	☐ Please take your XXX now. If you take more medications try setting up alarms on your phone at times medications are due. You are in control! ☐ Time to take your XXX now. Do you take more than one medication? Try organizing them in pill boxes. You can do it! ☐Your message
Take cancer tablets as part of a routine	☐ Please take your XXX now. Find a routine that makes it easy for you. You can do it! ☐ It's time to take your XXX. Taking your tablets as part of your daily routine can make it easier for you. ☐Your message
Worry about taking them for the rest of your life	☐ Time to take your XXX. Think about the health benefits of taking these tablets. You are in control of your treatment!

	☐ Please take your XXX now. Taking your tablets exactly as they were prescribed helps them work better. You can do it! ☐Your message
You feel well, don't have symptoms and your cancer is under control	☐ Time to take XXX. Even if you feel well and don't have symptoms taking your tablets is an important step towards achieving your long term health goals ☐ Please take XXX now. It is important to take it even if you feel well and don't have symptoms right now ☐Your message
Makes you feel worse	☐ Time to take XXX. Sometimes the tablets can make you feel worse in the short-term but it is important to take them to achieve your health goals ☐ Please take XXX now. If the tablets make you feel worse in the short-term talk to your doctor about the symptoms ☐Your message
Feel hassled about sticking to the treatment plan	☐ Time to take your XXX. If you feel hassled about sticking to the treatment plan remember that the tablets can help to reach your health goals ☐ Please take your XXX now. If you feel distressed about sticking to the treatment plan, think of the health benefits of taking your tablets. ☐Your message
Reminder and motivation	☐ It's time to take your XXX. You've done a great job all week of taking your tablets on time. Keep up the good work!. ☐ It's time to take your XXX. What a fantastic effort this week! Keep taking your tablets on time! ☐ Your message

Section 3. Information of chemotherapy, symptom management and intention of use

Topic A) Motivation to take cancer tablets

What motivates you to take your cancer tablets? (why do you take your cancer tablets)

Topic B) Intention to read short information about cancer tablets on smartphone

Information about cancer tablets is usually provided by health professionals when the medication is prescribed. In addition to that information, would you read short information about your cancer tablets from your phone?

B.1) Format of Information

If you received this information about your cancer tablets on your phone, how would you like it to be?

Prompt: A Video/ Text only/ Text and images

B.2) Preferred frequency of access to this information

How often would you read new information about your cancer tablets from your phone?

Topic C) Intention to read short information about skills to manage side-effects/symptoms on smartphone

As you know, cancer tablets can cause side-effects e.g. nausea, diarrhoea. Would you read short information about how to manage symptoms/side-effects caused by your cancer tablets from your phone?

C.1) Format of Information on symptom management

If you received information on how to manage symptoms/side-effects from your phone how would you like it to be?

Prompt: Video/ Text only/ Text and images

C.2) Preferred frequency of access to this information

How often would you read new information about how to manage cancer tablets symptoms/side-effects from your phone?

Topic D) Intention to use/recommend self-management program

(If the participant is currently taking oral chemotherapy) If you had the opportunity, would you like to receive text messages to help you take your cancer tablets? (If the participant is not currently taking oral chemotherapy) If you had the opportunity, would you recommend a friend to receive text messages to help him/her take the cancer tablets?

Do you have anything you would to add?

Thank you for your time.

I wish you all the best!!

Appendix E- Supplementary file paper 2. Included studies

n	Author/ year	Study purpose	Research Design	Participants	Mobile Phone Technology	Intervention	Main Findings
1	Spoelstra et al. 2016	To examine proof of concept of a text messages intervention and to conduct a preliminary evaluation of the efficacy of text messages with respect to adherence and symptom severity and interference in adult cancer patients prescribed oral anti-cancer agents.	Randomized controlled trial (2:1 allocation ratio), longitudinal (10 weeks).	75 participants newly prescribed oral chemotherapy or oral hormonal therapy with diverse types of cancers. Most common were: breast, prostate, lung, colon, and multiple myeloma. Recruited at two community cancer centres and a large specialty pharmacy in the United States of America.	Text message reminders.	21 days of short message service for adherence, control group received care as usual.	Differences in adherence between the experimental and control group were not statistically significant. Acceptability: 57% (83 of 145) of eligible participants consented to take part in the study, 88% (37/42 participants) in the experimental group read the text messages most of the time and 90% (38/42 participants) were satisfied with the intervention. Limitations: Challenges in the use of self-report tools to measure medication adherence as this relies on participants ability to recall medication intake.
2	Greer et al. 2017	To test the effect of a smartphone mobile app to improve adherence and symptom management in patients prescribed oral chemotherapy.	Randomized controlled trial with two groups, longitudinal (12 weeks).	181 patients with diverse cancers prescribed oral chemotherapy. United States of America.	A mobile phone app (designed for the study).	Intervention group: 12 weeks of using mobile app and usual care. Control group: usual care.	Study groups did not differ across outcome measures from baseline to week 12. Higher adherence scores Medication Event Monitoring System (MEMS) were observed in patients who reported adherence problems at baseline in experimental group compared to control group. Patients with higher anxiety assigned to the

							experimental group reported better adherence on the 12 week Morisky Medication Adherence Scale (MAAS) compared to standard care.
3	Fishbein et al. 2017	To develop and evaluate the usability and acceptability of a smartphone app to support adherence to oral chemotherapy and symptom management in patients with cancer.	Qualitative	32 stakeholders (cancer patients /caregivers, oncology clinicians, cancer practice administrators, representatives of community) 10 patients using oral chemotherapy (app's alfa testing). 5 patients using oral chemotherapy (app's beta testing). All in the United States of America.	Mobile phone app (designed for the study)	Focus groups with 32 stakeholders to inform the design of the app. Individual semi-structured interviews with 10 oral chemotherapy users and 8 oncology clinicians (alpha testing of app). Individual semi-structured interviews with 5 oral chemotherapy users (beta testing of app).	Stakeholders and patients who participated in alfa and beta trials of the app informed the inclusion of the following components in the app: medication reminders, self-reporting of medication adherence and symptoms, an education library including nutritional information, Fitbit integration, social networking resources, and individually tailored symptom management feedback. Usability and acceptability feedback during alfa and beta testing also informed the development of the app. Limitations: Quantitative usage and acceptability data during the development and preliminary testing phase, was not collected. The mobile app was only available for iPhone and Android operating systems, with potential to be modified in the

							future to include other operative systems.
4	Pereira-Salgado et al. 2017	To develop and pilot-test the clinical feasibility and acceptability of a mobile health system (REMIND) to increase oral drug adherence and patient symptom self-management among people with chronic myeloid leukaemia (chronic phase).	Qualitative, longitudinal (10 weeks)	10 patients with chronic myeloid leukaemia (chronic phase) and 2 nurses recruited from a cancer centre in Australia.	Text message reminders and web app.	Participants used the REMIND system for 10 weeks. The REMIND system consisted of daily text message reminders to take medication, weekly side-effect assessment online with automatically generated self-care advice and phone-based nurse consultation sessions.	Most patients indicated that receiving and responding to the text reminders prompted medication adherence due to accountability. The usability of the intervention was high. Most participants expressed ease with text message reminders and symptom report. Benefits reported by patients: help in establishing medication routines, resolution of symptom uncertainty, increased awareness of self-care, and informed decision making. Nurses also endorsed the intervention: it assisted in establishing pill-taking routines and patients developing effective solutions to adherence challenges. Limitations and recommendations: Failure to receive up to 40% text message reminders was reported by 2/9 patients who completed the pilot study. This was due to slow networks especially in remote areas. Data saturation might not have

							been reached due to sample size. This study included only patients diagnosed with chronic myeloid leukaemia. Future studies need to pilot this intervention in other cancer diagnosis.
5	Brett et al. 2018	To explore the feasibility of an app to improve adherence in women prescribed adjuvant endocrine therapy following breast cancer.	Qualitative (1 month)	20 women prescribed adjuvant endocrine therapy following breast cancer, recruited through the UK charity Breast Cancer Care and Independent Cancer Patients' Voice in the United Kingdom.	Mobile app (designed for study)	1 month trial of the app.	The app was found easy to download and use. Participants found the information section useful but expressed their willingness to receive more information on side-effect management. Links to evidence-based information and adjuvant endocrine therapy were perceived by participants as reassuring. Participants stated that recording their side effects in the app's diary helped them to manage their symptoms. Positive feedback was provided about medication reminders. Perceptions of the usefulness of a chat forum were mixed.

References:

1) Spoelstra SL, Given CW, Sikorskii A, et al. Proof of concept of a mobile health short message service text message intervention that promotes adherence to oral anticancer agent medications: a randomized controlled trial. Telemed J E Health. 2016 Jun; 22(6):497-506 PMID:26716365

Appendix F-Supplementary file paper 3. Symptom management toolkit’s modifications for the program

Symptom management toolkit's modifications for the program

Information features	Toolkit content modifications to suit the program
Information about symptoms (length and font size)	Each side-effect information to fit two to three pages (when possible) with a minimum of size 11 font.
Information about main oral chemotherapy-related symptoms	Include the 17 most common oral chemotherapy-related side effects: appetite (lack of), constipation, cough, diarrhoea, dry mouth, fatigue, fever, hand-foot syndrome, mouth sores, nausea/vomiting, numbness, pain, rash, shortness of breath, disturbed sleep, taste changes, and weakness.
Information about how to manage side-effects and what to report to healthcare professionals	Limit each piece of side-effect information to the following sections: what can I do about my side-effect?, what can family members and friends do to help me with my side-effect?, what should I report to my nurse or doctor about my side effect?, what should I discuss with my nurse or doctor about my side effect?, and where can I get more information?
Delivery of oral chemotherapy tailored information about symptoms	Information to be formatted as individual documents for each side-effect. To deliver program users information about the five main side-effects for their individual OC prescription
Focus on Australian users	Language adapted to Australian context

Appendix G-List of oral chemotherapy drugs

Oral Chemotherapy Drugs

(effective January 1, 2018)

ORAL CHEMOTHERAPY DRUGS

A

Afinitor (everolimus)
Alecensa (alectinib)
Alkeran (**melphalan**)
Alunbrig (brigatinib)
[redacted]

B

Bosulif (bosutinib)

C

Cabometyx (cabozantinib)
Caprelsa (vandetanib)
[redacted]
Cometriq (cabozantinib)
Cotellic (cobimetinib)
Cyclophosphamide (cyclophosphamide caps)

D

Droxia (hydroxyurea)

E

[redacted]
Erivedge (vismodegib)
etoposide

F

[redacted]
Farydak (panobinostat)
[redacted]

G

Gilotrif (afatinib)
Gleevec (**imatinib**)
Gleostine (lomustine)

H

Hexalen (altretamine)
Hycamtin (topotecan)
Hydrea (**hydroxyurea**)

I

Ibrance (palbociclib)
Iclusig (ponatinib)
Idhifa (enasidenib)
Imbruvica (ibrutinib)
Inlyta (axitinib)
Iressa (gefitinib)

J

Jakafi (ruxolitinib)

K

Kisqali (ribociclib)
[redacted]

L

Lenvima (lenvatinib)
leucovorin
Leukeran (chlorambucil)
Lonsurf (trifluridine/tipiracil)
Lynparza (olaparib)
Lysodren (mitotane)

M

Matulane (procarbazine)
[redacted]
Mekinist (trametinib)
mercaptopurine
Mesnex (mesna)
methotrexate
Myleran (busulfan)

N

Nerlynx (neratinib)
Nexavar (sorafenib)
Nilandron (**nilutamide**)
Ninlaro (ixazomib)

O

Odomzo (sonidegib)

P

Pomalyst (pomalidomide)
Purixan (mercaptopurine susp)

R

Revlimid (lenalidomide)
Rubraca (rucaparib)
Rydapt (midostaurin)

S

[redacted]
Sprycel (dasatinib)
Stivarga (regorafenib)
Sutent (sunitinib)

T

Tabloid (thioguanine)
Tafinlar (dabrafenib)
Tagrisso (osimertinib)
[redacted]
Tarceva (erlotinib)
Targretin (**bexarotene**)
Tasigna (nilotinib)
Temodar (**temozolomide**)
Thalomid (thalidomide)
tretinoin
Trexall (methotrexate)
Tykerb (lapatinib)

V

Venclexta (venetoclax)
Votrient (pazopanib)

X

Xalkori (crizotinib)
Xatmep (methotrexate soln)
Xeloda (**capecitabine**)
[redacted]

Z

Zejula (niraparib)
Zelboraf (vemurafenib)
Zolinza (vorinostat)
Zydelig (idelalisib)
Zykadia (ceritinib)
[redacted]

Brand names are capitalized and generic names are in lower case. ***Boldface*** *type indicates generic availability. Boldface may not apply to every strength or dosage form under the listed generic name. This list will be updated periodically. Refer to your Evidence of Coverage for details.*

To learn more about your specific drug benefit, log into *My Account* at **www.carefirst.com/myaccount** and click on Drug & Pharmacy Resources under Quick Links or call CareFirst Pharmacy Services at 800-241-3371.

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Appendix H- MEMS handling and delivery process for hospital oncology pharmacies

MEMS Handling and Delivery Process for Hospital Oncology Pharmacies

A small number of MEMS devices will be delivered by the research team and kept at the pharmacy.

These devices have been pre-activated. It is not necessary for you to re-do the activation process. Please read all of the information attached from the manufacturer about the MEMS device. This information is designed to help you become familiar with the device. However, please note that the primary purpose of the use of the device in this study is not to measure medication adherence, it is to explore participants' acceptability of the device and feasibility of its appropriate use in a future related study.

1) Study participants will provide consent to take part in the study and complete data collection questionnaires. Then they will be referred to the pharmacy for MEMS collection.
2) Participants will be told that the medication container tracks medication intake but that this is not the purpose of the device in this study. The purpose of the device is to explore if participants accept it and are satisfied with it. They will also be told that all participants will use the medication container to store cancer tablets in during the following 10 week period.
3) Please show the MEMS to participants and provide verbal instructions on how they should use it based on the participant instructions sheet. Please instruct them to store only one medication (the one provided by the pharmacy) in the MEMS device.
4) Address any questions they may have.
5) Please instruct participants to start using MEMS from the next due oral chemotherapy dose.
6) As the lids are active, they will track every opening as a medication intake event. Please do not open the lid when demonstrating the device to participants.
7) Proceed to re-fill MEMS with participants' prescription. Label the bottle as usual with the patient and drug information. The MEMS lid is child resistant. Please try to open the lid just once during this process.
8) If tablets are packed in blisters cut the blisters to fit into the MEMS (do not take medication out of the original blister).
9) Deliver the filled/labelled MEMS to the participant and instruct them to bring the MEMS to their next pharmacy visit for re-fill. Provide participants with the printed, 2-page participant information brochure.
10) Register date and time of MEMS re-fill for each participant in the document provided for this purpose.
11) Please let participants know that they should ONLY attend this pharmacy for oral chemotherapy prescriptions re-fills during the next 10 weeks (This information is also provided to participants in the study information sheet).
12) **Please immediately notify the lead researcher Xiomara Skrabal Ross** (Xiomara.skrabal_ross@mymail.unisa.edu.au) **that the participant received filled MEMS**. The researcher will proceed to activate the text-message based intervention for the participant.
13) At the end of the study (week 10) participants will be instructed to return the MEMS to the pharmacy when they go to fill their next prescription. If any tablets are left in the device please provide the participant with an adequate container to keep those tablets in. Please ensure the MEMS device has the cap on and store it separately from any unused MEMS devices. There is no need to re-label the device
14) The researcher will collect the used MEMS fortnightly and provide more unused devices if necessary.
15) **Please do not re-use MEMS devices** with different participants. Data will be mixed-up and cross-contamination of different drugs is a risk highlighted by the manufacturer.
16) If you have any questions please contact the lead researcher Xiomara Skrabal xiomara.skrabal_ross@mymail.unisa.edu.au ph: 0410900975 (please do not provide this phone number to participants).The phone number for participants to call is 08 8302 2137 (Dr Kate Gunn).

Appendix I- How to use your new medication container. Instructions for study participants

How to use your new medication container

Instructions for study participants

1) You will use the medication container to store your cancer tablets in during the course of this study (10 weeks). All participants in this study will receive one.
2) To open the tablet container turn the lid counter-clockwise, similar to a child-proof lid used in other medications (push down and turn).



3) Now the lid can be easily removed from the bottle.



4) Take a medication blister or the pill/s from the bottle
5) You can now take your medication.



6) To close the medication container turn clockwise (push and turn).

Special Remarks:

- When you receive the medication container **please start using it to take your next due oral cancer medication dose.**
- Please do **NOT open the container unnecessarily**.
- No other dosing dispenser (e.g. pill organizer) should be used besides the medication container with the lid. No pocket dosing.
- Do not place any other medication in the container.
- Promptly close the container with the lid after removing each dose. Never leave the medication container with the lid open.
- Do not immerse the lid in any liquid; do not clean it with detergent or alcohol. The exterior may be wiped with a slightly damp cloth.
- Always bring the container with the lid to each visit to the hospital pharmacy. During the time of the study (10 weeks). **During the course of the study you will only be able to obtain further supplies of your medication from the same hospital pharmacy**

Appendix J- Assessment tools

Name:_____

Socio-Demographic and Oral Cancer Medication Questionnaire

This questionnaire collects personal information that help us to understand the characteristics of our study participants. It also ask questions about your oral cancer medication treatment that allow to tailor the text message program to your individual needs.

Please answer all the questions. Do not leave questions blank. If you are unsure on how to answer a question please see a staff member.

Demographics and selection criteria

1. **Do you currently suffer from any conditions that affect your judgement (e.g. dementia, psychosis)?**

☐*Yes* ☐*No*

2. **If the answer is Yes, what is the name of the condition?** _____

(if the answer is yes, potential participant will be informed that the presence of such condition is an exclusion criteria for this study)

3. **What is your gender?** ☐*Male* ☐*Female* Other_____

4. **What is your age (in whole years from your last birthday)?** _____

5. **What is your marital status?**

☐ *Married or living with a partner*
☐ *Separated/ divorced*
☐ *Widowed*
☐ *Never married*

6. **What is your highest educational qualification you have completed?**

☐ *Did not finish primary school*
☐ *Finished primary school*
☐ *Finished high school*
☐ *Trade certificate, apprenticeship, diploma or certificate from a college or TAFE*
☐ *Degree or diploma from a university*
☐ *Postgraduate degree*

7. **What is your employment situation?**

☐ *Full-time employment*
☐ *Part-time employment*
☐ *Casual employment*
☐ *Not employed and not looking for a job*
☐ *Not employed and looking for a job*
☐ *Retired*

8. **Do you own a smartphone (a device that combines a cell phone with a handheld computer, typically offering Internet access, data storage, email capability, etc)?**

☐*Yes* ☐*No*

9. **Are you able to access internet connection at least once a week?**

☐*Yes* ☐*No*

10. **Are you willing to receive and read text messages on your phone sent by the research team?**

☐ *Yes*
☐ *No*
☐ *Not sure (please talk to a staff member)*

11. **Are you currently taking prescribed oral cancer medication?**

☐*Yes* ☐*No*

12. **Is it expected that you will take the cancer medication for at least the next 3 months?**

☐*Yes* ☐*No*

13. **Are you currently taking part in any research that is focused on helping you to improve the way you take your cancer medication?**

☐*Yes* ☐*No*

Oral cancer tablets

14. **What is your cancer diagnose?** _____

15. **When were you diagnosed? (month/year)**_____

16. **What is the name of the oral cancer medication you currently take?** _____

17. **How often do you take this cancer medication?**

☐ *Once a day*
☐ *Twice a day*
☐ *Other* _____

18. **At what time do you take your oral cancer medication?** _____☐AM ☐PM

19. **If you take your cancer medication in cycles (eg. 2 weeks in, 1 week off) please explain the cycle and tell us the date of your last dose in this cycle and the date you are due to re-start the cycle.**

_____

20. **As part of this study you will receive information on your phone about your oral cancer medication and how to manage the main 5 side-effects.**

How often would you like to receive new information?

☐ *Once a week*
☐ *Once a fortnight*
☐ *Once a month*
☐ Only one time a*t the beginning of the study*

Thank you!

Name: ____ _____

Knowledge of Oral Cancer Medication Survey

This survey was designed to explore what you know about your oral cancer medication treatment. Please answer all of the questions. We are interested in your honest answers. Thank you for participating!

1) Do you know the name of your oral cancer medication?
   ☐Yes
   ☐No

2) If yes, what is the name of your oral cancer medication? __ _____

3) Do you know when to take your cancer medication?
   ☐
   ☐No

4) If yes, when do you take your medication? __ _____

5) Do you know how many cancer tablets (pills) to take?
   ☐
   ☐No

6) If yes, how many will you take? _____

7) For how long (months/weeks) do you need to take your oral cancer medication?
   _____

8) Does it matter if you take your medication with food?
   ☐Yes
   ☐No

9) Where do you keep your oral cancer medication? (e.g. kitchen cupboard)

_____

_____

_____

10) What are the main side-effects you can expect to experience from taking your oral cancer medication?

_____

_____

Thank you!

Name:_____ _____

Questions about using your Oral Cancer Medication

Many people find a way to use their oral cancer medication that suits them.

This may differ from the instructions in the label and from what their doctor has said.

We would like to ask you a few questions about how you use your oral cancer medication.

Here are some ways in which people have said that they take their cancer medication For each of the statements, please tick the box that best applies to you

1) I forget to take my cancer medication ☐*Yes* ☐*No*

2) I change the dosage of my cancer medication ☐*Yes* ☐*No*

3) I stop taking my cancer medication for a while ☐*Yes* ☐*No*

4) I decide to skip one of my cancer medication dosages ☐*Yes* ☐*No*

5) I use my cancer medication less than it is prescribed ☐*Yes* ☐*No*

The Medication Adherence Report Scale (MARS-5) was created by Dr. Robert Horne

Name:_____

Symptom Presence and Severity Scale

The following list includes common symptoms related to the use of oral cancer medication. Symptoms vary between individuals and you may or may not have experienced them during your treatment. In this scale "0" means that you did not experience the symptom and "5" represents the worst severity of the symptom.

Please tick the appropriate number for the symptoms you have experienced in the **last 2 weeks**.

	0	1	2	3	4	5
	No symptom	Very Mild	Mild	Moderate	High	Severe
Diarrhoea						
Nausea/vomiting						
Fatigue						
Cough						
Constipation						
Weakness						
Lack of appetite						
Fever						
Pain						
Hand-foot Syndrome						
Mouth sores						
Dry mouth						
Numbness and tingling						
Skin rash/sores						
Shortness of breath						
Taste changes						
Disturbed sleep						

Name:_____

Satisfaction Survey

Please help us improve our program by answering some questions. We are interested in your honest opinions, whether they are positive or negative. *Please answer all of the questions*. We also welcome your comments and suggestions. Thank you very much, we appreciate your help.

1) How satisfied are you overall with your participation in the study?
   ☐Not at all
   ☐Somewhat
   ☐Very much
   ☐Highly

2) Did you have any problems with the text message system?
   ☐Yes ☐No

   If yes, please describe the problems_____
   _____
   _____
   _

3) Did you have any problems accessing the information about oral cancer medication and symptom management?
   ☐Yes ☐No

   If yes, please describe the problems
   _____
   _____
   _____

4) Overall, for you personally, the text messaging was
   ☐Mostly helpful
   ☐Neutral
   ☐Not helpful

5) The information about your oral cancer medication and symptom management was
   ☐Very helpful
   ☐Helpful
   ☐Somewhat helpful
   ☐Not helpful

6) Did the text messages help you take your cancer medication on time?
   ☐Helped
   ☐Neutral
   ☐Did not help

7) How satisfied were you with text reminders to take your medications?
   ☐Not at all
   ☐Somewhat
   ☐Very much
   ☐Highly

8) How satisfied were you with the information about your oral cancer medication and symptom management?
   ☐Not at all
   ☐Somewhat
   ☐Very much
   ☐Highly

9) Did you read the text message medication reminders?
   ☐All of the time
   ☐Most of the time
   ☐Some of the time
   ☐None of the time

10) Did you read the information about your oral cancer medication and symptom management?
   ☐All of the time
   ☐Most of the time
   ☐Some of the time
   ☐None of the time

11) Would you recommend text messages as a reminder to take your cancer medication?
   ☐Yes ☐No

12) Would you recommend the smartphone program (text messages and information) to other people who have been prescribed cancer medication?
   ☐Yes ☐No

13) Did you use the medication container provided in the study during all 10 weeks?
   ☐Yes ☐No

14) Did you find any challenges in using the medication container?
   ☐Yes ☐No

15) Please explain the challenges:
   _____
   _____
   _____

Comments:

Appendix K- Michigan State University. Material transfer agreement

MICHIGAN STATE UNIVERSITY
MATERIAL TRANSFER AGREEMENT
Non-profit/Educational Institution

In consideration of the mutual covenants contained herein and with the intention of being legally bound under the laws of the State of Michigan, the parties agree as follows:

1. The Parties to this Agreement are: Michigan State University, 325 East Grand River, Suite 350, East Lansing, Michigan 48823 (hereinafter referred to as "MSU") and University of South Australia, Division of Health Sciences, City East Campus, Adelaide SA 5001 (hereinafter referred to as "RECIPIENT")

2. The material covered by this Agreement is defined as and includes the following: Symptom Management Toolkit (for reference only TEC2003-0090), (hereinafter referred to as "MATERIAL") developed by Barbara Given, Ph.D., Charles Given, Ph.D., Cindy Majeske at MSU.

3. RECIPIENT agrees that MATERIAL will not be disclosed in violation of any applicable export control regulations. RECIPIENT agrees that MATERIAL shall be used in accordance with the Purpose (as defined below) and shall not be released to any person other than the RECIPIENT Scientist, those working directly under the Recipient Scientist's supervision who have agreed to abide by the terms and conditions of this Agreement and participants in the GRANT (as defined below) and subjects enrolled in the study described in the Purpose. Except as provided in the GRANT, no one is permitted to take or send this MATERIAL to any other location, unless prior written permission is obtained from MSU; such permission will not be withheld unreasonably.

4. This Agreement and the resulting transfer of MATERIAL constitute a restricted license for RECIPIENT to use the MATERIAL solely for the following research purposes: "Purpose" shall mean RECIPIENT's use of MATERIAL for an upcoming research study sponsored by RECIPIENT entitled "Effect of Smartphone Self-Management Program on Adherence to Oral Chemotherapy in AYA and Adult Cancer Patients", which is scheduled to run approximately two (2) years from March 2018 thru March 2020 ("GRANT"). MATERIAL will not be used for any purpose inconsistent with this Agreement. Commercial use of this MATERIAL is strictly prohibited. Nothing in this Agreement grants RECIPIENT any additional rights, either expressed or implied, to MSU patents, trademarks, copyrights, know-how, or other intellectual property. Upon completion of the Purpose, RECIPIENT shall cease using MATERIAL and shall delete all third-party access to same. MSU retains title to the MATERIAL and RECIPIENT shall not obtain any ownership rights in MATERIAL. MATERIAL is experimental in nature and it is provided WITHOUT WARRANTY OF ANY SORT, EXPRESSED OR IMPLIED, INCLUDING WITHOUT LIMITATION WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR USE. MSU makes no representation and provides no warrant that the use of the MATERIAL will not infringe any patent or proprietary rights of third parties.

5. RECIPIENT assumes all liability for damages that may arise from its use or distribution of the MATERIAL. MSU will not be liable to the RECIPIENT for any loss, claim or demand made by the RECIPIENT, or made against the RECIPIENT by any other party, due to or arising from the use of the MATERIAL by the RECIPIENT, except to the extent permitted by law when caused by the gross negligence or willful misconduct of MSU.

   MATERIAL should not be considered medical advice or a substitute for medical advice and RECIPIENT shall include a similar statement in any distribution or use of MATERIAL, including but not limited to, utilization of MATERIAL in the performance of GRANT.

6. RECIPIENT agrees that it will follow all applicable guidelines, laws, regulations, and government agency guidelines regarding the use of MATERIAL.

7. If the RECIPIENT desires to use or license the MATERIAL for commercial purposes, the RECIPIENT agrees, in advance of such use, to negotiate in good faith with MSU to establish the terms of a commercial license. It is understood by the RECIPIENT that MSU shall have no obligation to grant such a license to the RECIPIENT, and may grant exclusive or non-exclusive commercial licenses to others, or sell or assign all or part of the rights in the MATERIAL to any other third-party(ies), subject to any pre-existing rights held by others and obligations to the United States Government.

8. RECIPIENT hereby agrees to provide MSU with a report of observations related to the MATERIAL by providing MSU with a report describing the results of such research using the MATERIAL. To the extent that it is able, RECIPIENT Scientist will acknowledge MSU's contribution in all publications and presentations based on the use of the MATERIAL.

9. RECIPIENT hereby grants MSU a nonexclusive, royalty-free right to use for MSU's internal research purposes any information or new material developed by RECIPIENT using MSU MATERIAL. In any publication involving RECIPIENT's information or material, MSU agrees to cite its source and give credit of authorship/creatorship to RECIPIENT.

10. This Agreement will terminate on the earliest of the following dates: (1) on completion of RECIPIENT's current research with the MATERIAL, (2) on thirty (30) days written notice by either party to the other, or (3) three (3) years from the date of last signing.

11. Clauses 4 and 5 shall survive termination of this Agreement.

12. This Agreement shall be executed by all Parties through a duly authorized representative and shall be effective as of the date of last signing.

Signature Page Follows

MICHIGAN STATE UNIVERSITY

By: [redacted]

Richard W. Chylla, Ph.D.
Executive Director
MSU Technologies

325 East Grand River
Suite 350
East Lansing, Michigan 48823

Date: 2/1/18

RECIPIENT: UNIVERSITY OF SOUTH AUSTRALIA

By: [redacted]

Ian Olver
Director
Sansom Institute for Health Research

Division of Health Sciences
P5-06e Playford Building
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Date: 1-02-2018

Read and acknowledged by:

MICHIGAN STATE UNIVERSITY
Scientist

By: [redacted]

Typed Name: Dr. Barbara Given

Title: University Distinguished Professor Emerita

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Bott Building for Nursing Education and Research
1355 Bogue Street
East Lansing, MI 48824

Date: 2/1/2018

Read and acknowledged by:

RECIPIENT
Scientist

By: [redacted]

Typed Name: Xiomara Skrabal Ross

Title: Ph.D. Student

Address:

School of Health Sciences
University of South Australia
City East Campus
Adelaide SA 5001

Date: 01/02/2018

Appendix L- Example of information about oral chemotherapy and information about side-effects for the drug dasatinib

The treatment schedule below explains how the drug for this treatment is given, what it looks like and how to store it.

Generic name: DASATINB		Trade name: Sprycel
This treatment is continuous. Your doctor will advise you how long to take the treatment for.		
Day	**Treatment**	**What it looks like**
Continuous	**Dasatinib** *(duh-sat-in-nib)*	Sprycel 20 mg: white to off-white, biconvex, round tablet with "BMS" debossed on one side and "527" on the other Sprycel 50 mg: white to off-white, biconvex, oval tablet with "BMS" debossed on one side and "528" on the other Sprycel 70 mg: white to off-white, biconvex, round tablet with "BMS" debossed on one side and "524" on the other Sprycel 100 mg: white to off-white, biconvex, oval film-coated tablet with "BMS 100" debossed on one side and "852" on the other
		How it is given
		Take orally ONCE a day, at the same time each day, with or without food. Swallow whole with a large glass of water, do not break, crush or chew. If you are taking an antacid, do not take within two hours as this may interfere with its absorption. If you forget to take a dose or vomit a dose, take your normal dose the next time it is due. Do not take an extra dose.
		How to store it
		Keep your tablets in their pack until it is time to take them. If you take the tablets out of their bottle or blister they may not keep well. Keep your tablets in a cool dry place where the temperature will stay below 30°C. Do not store your medicine, or any other medicine, in the bathroom or near a sink. Do not leave it on a window sill or in the car. Heat and dampness can destroy some medicines. Keep it where children cannot reach it. A locked cupboard at least one-and a-half metres above the ground is a good place to store medicines.

Information taken from eviQ (www.eviq.org.au) and Consumer Medicine Information (Australian Government, Department of Heath)

This document is a guide only and cannot cover every possible situation. The health professionals caring for you should always consider your individual situation when making decisions about your care. Contact your cancer clinic staff or doctor if you have any questions or concerns about your treatment, or you are having problems coping with side effects.

General Advice for People having Cancer Treatment

Medications and vaccinations

- Before you start treatment, tell your doctor about any medications you are taking, including vitamins or herbal supplements.
- Don't stop or start any medications during treatment without talking to your doctor and pharmacist first.
- Paracetamol is safe to take if you have a headache or other mild aches and pains. It is recommended that you avoid taking aspirin, ibuprofen and other anti-inflammatory type medications for pain while you are having treatment. However, if these medications have been prescribed by your doctor, do not stop taking them without speaking with your doctor.
- Vaccinations such as flu and tetanus vaccines are safe to receive while having treatment. Do not have any live vaccines during your treatment or for 6 months after it finishes. If you are unsure, check with your doctor before you have any vaccinations.
- People you live with should be fully vaccinated, including having live vaccines according to the current vaccination schedule. Extra care needs to be taken with hand washing and careful disposal of soiled nappies for infants who have recently received the rotavirus vaccine.

Other medical and dental treatment

- If you go to hospital or any other medical appointment (including dental appointments), always tell the person treating you that you are receiving anticancer drugs.
- Before you have any dental treatment, talk to your doctor.

Diet and food safety

- While you are receiving this treatment, it is important that you try to maintain a healthy diet.
- Grapefruit and grapefruit juice can interact with your medication and should be avoided while you are on this treatment.
- Speak to your doctor or nurse about whether drinking alcohol is safe with your treatment.
- If you have any concerns about recent weight loss or weight gain or questions about your diet, ask to speak to a dietitian.
- There are some foods that may cause infection in high risk individuals and should be avoided (see www.eviq.org.au for the listeria and food brochure)

Fertility

- Some cancer treatments can reduce your fertility. This can make it difficult or impossible to get pregnant or father a child.
- Talk to your doctor or nurse before you start any treatment. Depending on your situation there may be fertility sparing options available to you and/or your partner, discuss these with your doctor or nurse.

Pregnancy and breastfeeding

- Some cancer treatments can be dangerous to unborn babies. Talk to your doctor or nurse if you think there is any chance that you could be pregnant.
- Do not try to get pregnant or father a child during this treatment. Ask your doctor or nurse about what type of contraception you should use.
- Do not breastfeed if you are on this treatment as anticancer drugs can also pass into breast milk.

Sex life and sexuality

- The desire to have sex may decrease as a result of this treatment or its side effects.
- Your emotions and the way you feel about yourself may also be affected by this treatment.
- It may help to discuss your concerns with your partner and doctor or nurse.

Blood clot risk

- Cancer and anticancer drugs can increase the risk of a blood clot (thrombosis).
- Tell your doctor if you have a family history of blood clots.
- A blood clot can cause pain, redness, swelling in your arms or legs, shortness of breath or chest pain.
- If you have any of these symptoms go to your nearest hospital Emergency Department.

Information taken from eviQ (www.eviq.org.au)

This document is a guide only and cannot cover every possible situation. The health professionals caring for you should always consider your individual situation when making decisions about your care. Contact your cancer clinic staff or doctor if you have any questions or concerns about your treatment, or you are having problems coping with side effects.

Side effects

Cancer treatments can cause damage to normal cells in your body, which can cause side effects. Everyone gets different side effects, and some people will have more problems than others.

The table below shows some of the side-effects you may get with this treatment. You are unlikely to get all of those listed and you may also get some side effects that have not been listed.

Tell your doctor or nurse about any side effects that worry you.

Immediate (onset hours to days)

Nausea and vomiting

Headache

Taste and smell changes

Early (onset days to weeks)

Infection risk (neutropenia)

Low platelets (thrombocytopenia)

Diarrhoea

Tiredness and lack of energy (fatigue)

Stomach pain

Bleeding (haemorrhage)

Nerve damage (peripheral neuropathy)

Joint and muscle pain and stiffness

Skin rash

Heart problems

Extra fluid in the body (fluid retention)

Hearing changes (ototoxicity)

Late (onset weeks to months)

Low red blood cells (anaemia)

Depression

Hair thinning

Information taken from eviQ (www.eviq.org.au)

This document is a guide only and cannot cover every possible situation. The health professionals caring for you should always consider your individual situation when making decisions about your care. Contact your cancer clinic staff or doctor if you have any questions or concerns about your treatment, or you are having problems coping with side effects.

When to Get Help

Anticancer drugs (drugs used to treat cancer) can sometimes cause serious problems. It is important to get medical help immediately if you become unwell.

IMMEDIATELY go to your nearest hospital Emergency Department, or contact your doctor or nurse if you have any of the following at any time:	**Emergency contact details** Ask your doctor or nurse from your treating team who to contact if you have a problem
• a temperature of 38°C or higher • chills, sweats, shivers or shakes • shortness of breath • uncontrolled vomiting or diarrhoea • pain, tingling or discomfort in your chest or arms • you become unwell.	Daytime: _____ Night/weekend: _____ Other instructions: _____ _____ _____

Information taken from eviQ (www.eviq.org.au)

This document is a guide only and cannot cover every possible situation. The health professionals caring for you should always consider your individual situation when making decisions about your care. Contact your cancer clinic staff or doctor if you have any questions or concerns about your treatment, or you are having problems coping with side effects. Use of this document is subject to eviQ's disclaimer available at www.eviQ.org.au

Diarrhoea

(This information does not intent to replace medical advice. If you have any questions you would like to discuss with your doctor or nurse, please contact them directly).

What can I do about diarrhoea?

Here are some tips you may find helpful:

ACTIVITY

- Keep track of the number of stools you have within a 24 hour period. Also, record any cramping or gas pains in a diary.
- Diarrhoea can cause pain and soreness to the skin around the rectum. Clean the area often with unscented baby oil or baby wipes. The aloe in baby wipes can be very soothing. Use the wipes instead of toilet paper to gently wipe the rectal area. Rinse well and pat dry with a soft towel. Cleaning decreases the risk of infection and skin irritation.
- Take warm baths 3-4 times a day. Sit in the warm water for about 10 minutes to relieve lower body discomfort.
- Use a thick, protective lotion ointment on the skin after each bowel movement.

COMMUNICATION

- Contact your nurse or doctor to prescribe something for your diarrhoea if over-the counter-medications do not work.
- Let your nurse or doctor know if you have tears in the skin around the rectum.

DIET

- Try eating smaller, more frequent meals or snacks (5-6 per day) instead of 3 large meals.
- Try eating foods such as bananas, white rice, oats, applesauce, smooth peanut butter, bland biscuits, dry toast, biscuits, plain pasta, eggs, cheese, boiled chicken, fish, cooked carrots, poultry or baked potatoes. Choose foods high in protein, calories and potassium that are easy to digest.
- Eat bland, low-fibre foods/avoid eating food that is high in fibre (granola, bran, whole wheat) or food that is fatty or spicy. Try not to eat rich desserts and avoid foods that are very high in fat. Examples of foods that can increase bowel movements or gas include: beans, raw vegetables, cabbage, corn, cauliflower, broccoli, and chillies.
- Avoid spicy, greasy and fried foods. This includes most fast food.
- Add nutmeg to foods in order to slow down the movement through the intestines.
- Do not drink alcoholic beverages.
- Follow a low fibre/ low roughage diet. Do not eat wheat and bran.
- Avoid raw fruits and vegetables or foods high in insoluble fibre.
- Drink 8 glasses (240 ml.) daily of fluid to keep hydrated. Fluids can include water, lemonade, lemon-lime soda, icy poles, broth or soups. or soup broth. Avoid caffeine (i.e. colas, coffee, tea, energy drinks) when possible. Caffeine can cause dehydration.
- Replace lost electrolytes with nonfat clear broth, soup, gelatin, orange juice, Hydralyte or Grastrolyte (often available at medical supply stores) or sports drinks like Gatorade. You can also drink diluted fruit juice (half juice-half water).

- Try to drink fluids at room temperature. Hot and cold food may aggravate diarrhoea.
- Clear liquids may be easier to tolerate. Try clear fruit juices like apple or cranberry, ginger ale and jelly
- When having diarrhoea, drink less fluid with your meals. Drink more fluid between meals and avoid very hot and cold liquids.
- Avoid nuts and dried fruits.
- Avoid milk products (including ice cream, sour cream and cheese) until diarrhoea subsides.

- Try cottage cheese, cream of wheat, or plain yogurt.
- Avoid substances that contain sorbitol, such as sugar-free candy and sugar-free gum.

MEDICATIONS

- You should not take any over-the-counter medications while receiving chemotherapy or taking oral cancer medications without discussing them with your doctor or nurse first. This is because diarrhoea can be caused by an infection or due to a medication you are receiving. Your nurse or doctor will want to determine this before you take any medication to stop the diarrhoea, and may give you instructions for taking the medications that are different from those on the package.
- Talk to your nurse or doctor about taking over-the-counter medications, such as Imodium AD, Kaopectate, Pepto-Bismol or loperamide.
- Talk to your nurse or doctor before using any creams or ointments if you are receiving radiation treatments to the abdomen, pelvis, or rectal area.

What can my family members and friends do to help me with my diarrhoea?

Ask family members and friends to:

- Buy food that can help decrease diarrhoea (see Diet).
- Remind you to take your over-the-counter medicines as directed.
- Prepare low fibre meals.
- Offer you fluids and broth throughout the day.
- Assist in locating restrooms when outside your normal environment.
- Help with keeping a log or record of your bowel movements and symptoms. This log or record will help your nurse or doctor better understand and treat your diarrhoea. Try to record the number of stools, time of day, whether stools were formed or watery, any cramping you experienced, and your daily weight. Also record if any medication was taken and fluid intake.

What should I report to my nurse or doctor about my diarrhoea?

Diarrhoea should not be ignored, since it can result in loss of fluid and nutrition and can be uncomfortable. If you experience any of the following symptoms, report them to your nurse or doctor.

- Skin around the rectum that is open, sore, tender or bleeding.
- Any new fever. If you have a **low white blood count** a fever is defined as having three readings of oral temperatures above 38º C in a 24 hour period, or one oral temperature reading above 38.5º C; this should be reported to your nurse or doctor immediately. If you **do not have a low white blood count** then fevers of 38.3º C or above should be reported if it persists beyond 24 hours. Make sure that when you take your temperature, you have not had any hot or cold drinks in the last 10-15 minutes.
- Report to your nurse or doctor about diarrhoea that continues for more than 24 hours.
- Bloody or black, tarry-looking stools.
- Unable to eat or drink for more than 24 hours.
- Diarrhoea that continues for more than 3 days.
- Being thirsty.
- Feeling tired or dizzy/fainting.
- Weakness.
- Urinating less often than usual.
- Having dark yellow colored urine.
- Severe abdominal cramps or pain for more than 3 days.
- Heart palpations (heart racing when you are at rest).

- Have your log or record available with the following information:
  - Your normal bowel pattern.
  - Color, consistency, and number of stools in the last 24 hours.
  - How much food and fluid you have taken in the last 1-2 days.
  - Medicines that you have taken in the last 2-3 days.
  - Any history of past bowel problems.
  - If you are being treated with radiation therapy to the pelvis, abdomen, or rectum.
  - Weight loss.

What should I discuss with my nurse or doctor about my diarrhoea?

If you are experiencing diarrhoea, you should discuss the following with your nurse or doctor at your next appointment:

- Have your log or record available with the following information:
  - Your normal bowel pattern.
  - Color, consistency, and number of stools in the last 24 hours.
  - How much food and fluid you have taken in the last 1-2 days.
  - Medicines that you have taken in the last 2-3 days.
  - Any history of past bowel problems.
  - If you are being treated with radiation therapy to the pelvis, abdomen, or rectum.
  - Weight loss.
- Does my cancer medication cause diarrhoea? If so, how is it usually controlled?
- What medications can I take?
- How long does the diarrhoea usually last?
- Do I need to be on a low fibre diet?
- When do you want me to notify you if I develop diarrhoea?

Where can I get more information?

For more information, visit the websites listed below:

- EviQ at **www.eviq.org.au** Click on “Patients and Carers”, then click on “Patient Information Sheets” scroll down and click on “Diarrhoea during cancer treatment”.

- American Cancer Society at **www.cancer.org** Click on the purple “Find Support & Treatment” tab at the top, then click on “Treatment and Side Effects” on the left. Scroll down and click on “Physical Side Effects”. Scroll down again to select “Dealing with Symptoms at Home”. Select “Diarrhea”.

- National Cancer Institute at **www.cancer.gov** Select “Gastrointestinal Complications (PDQ)” and then click on the “Patient Version” tab.

Information taken from: Symptom Management Toolkit. Michigan State University. ©Michigan State University Board of Trustees.

Appendix M- Satisfaction questionnaire scores by age group and gender

Satisfaction questionnaire scores by age group and gender

	Moderate satisfaction scores				High satisfaction scores								
	30 (n)	31 (n)	32 (n)	33 (n)	34 (n)	35 (n)	36 (n)	37 (n)	38 (n)	39 (n)	40 (n)	41 (n)	42 (n)
Total sample (N=21) (mean=36.76, median=37, SD=3.56)	1	1	1	1	2	2	2	1	2	2	2	3	1
Age group (p=.231)													
16-25 y/o (N=3) (mean=37.33, SD=1.52)	-	-	-	-	-	-	1	1	-	1	-	-	-
26-50 y/o (N=4) (mean=35.50, SD=3.00)	-	-	1	-	1	-	-	-	2	-	-	-	-
51-60 y/o (N=7) (mean=37.42, SD=3.86)	-	1	-	-	1	-	1	-	-	1	1	2	-
61-75 y/o (N=7) (mean=36.27, SD=4.50)	1	-	-	1	-	2	-	-	-	-	1	1	1
Gender (p=.150)													
Female (N=11) (mean=36.45, SD=3.69)	-	1	1	-	2	2	-	-	1	1	-	3	-
Male (N=10) (mean=37.1, SD=3.57)	1	-	-	1	-	-	2	1	1	1	2	-	1

Appendix N- Responses to the items in the satisfaction questionnaire by age group and gender

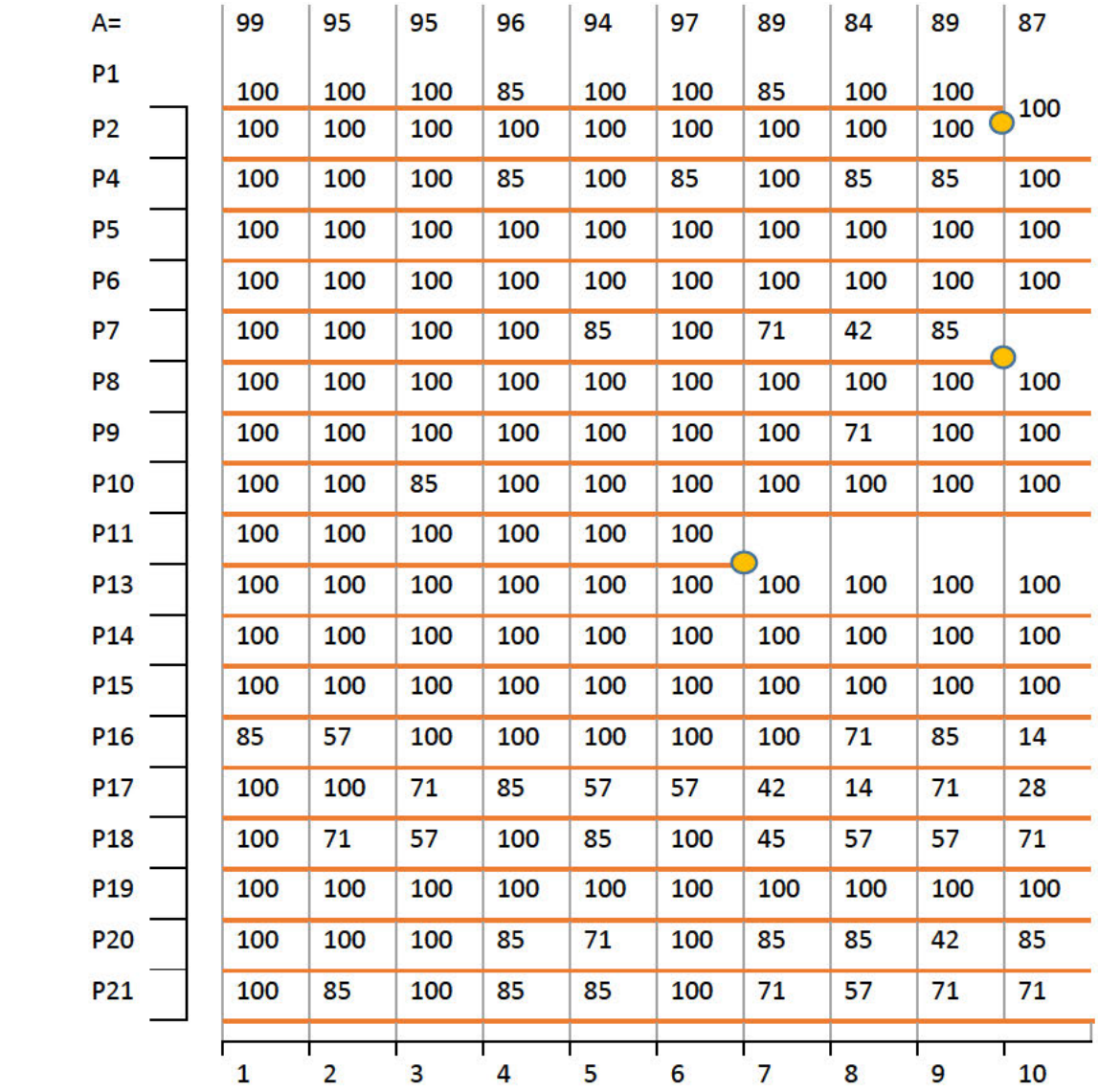
Responses to the items in the satisfaction questionnaire by age group and gender

	Total N=21		Age group (years)				Gender	
Item	n	%	16-25 (n=3)	26-50 (n=4)	51-60 (n=7)	61-75 (n=7)	female (n=11)	male (n=10)
1. How satisfied are you overall with your participation in the								
Not at all	0	0	-	-	-	-	-	-
Somewhat	2	9.52	-	1	-	1	1	1
Very much	8	38.1	-	3	2	3	5	3
Highly	11	52.38	3	-	5	3	5	6
2. Did you have any problems with the text message system?								
Yes	0	0	-	-	-	-	-	-
No	21	100	3	4	7	7	11	10
3. Did you have any problems accessing the information about oral cancer medication and								
Yes	1	4.76	-	-	1	-	1	-
No	20	95.24	3	4	6	7	10	10
4. Overall, for you personally, the text messaging was								
Mostly helpful	18	85.71	3	3	6	6	9	9
Neutral	2	9.52	-	0	1	1	1	1
Not helpful	1	4.76	-	1	-	-	1	0
5. The information about your oral cancer medication and								
Very helpful	10	47.62	2	2	5	1	4	6
Helpful	8	38.1	-	2	-	6	5	3
Somewhat helpful	3	14.29	1	-	2	-	2	1
Not helpful	0	0	-	-	-	-	-	-
6. Did the text messages help you take your cancer medication on								
Helped	17	80.95	3	3	6	5	9	8
Neutral	3	14.29	-	-	1	2	1	2
Did not help	1	4.76	-	1	-	-	1	-
7. How satisfied were you with text reminders to take your								
Not at all	0	0	-	-	-	-	-	-
Somewhat	4	19.05	-	-	1	3	2	2
Very much	7	33.33	-	3	3	1	5	2
Highly	10	47.62	3	1	3	3	4	6
8. How satisfied were you with the information about your oral cancer medication and symptom								

Not at all	1	4.76	-	-	1	-	1	0
Somewhat	3	14.29	-	-	1	2	2	1
Very much	7	33.33	1	3	2	1	3	4
Highly	10	47.62	2	1	3	4	5	5
9. Did you read the text message medication reminders?								
All of the time	7	33.33	-	1	3	3	4	3
Most of the time	11	52.38	2	2	4	3	6	5
Some of the time	3	14.29	1	1	-	1	1	2
None of the time	0	0	-	-	-	-	-	-
10. Did you read the information about your oral cancer medication								
All of the time	7	33.33	-	2	2	3	4	3
Most of the time	7	33.33	-	1	3	3	5	2
Some of the time	6	28.57	2	1	2	1	2	4
None of the time	1	4.76	1	-	-	-	-	1
11. Would you recommend text messages as a reminder to take								
Yes	21	100	3	4	7	7	11	10
No	0	0	-	-	-	-	-	-
12. Would you recommend the smartphone program (text messages and information) to								
Yes	21	100	3	4	7	7	11	10
No	0	0	-	-	-	-	-	-
13. Did you use the medication container provided in the study								
Yes	21	100	3	4	7	7	11	10
No	0	0	-	-	-	-	-	-
14. Did you find any challenges in using the medication container?								
Yes	4	19.05	-	2	-	2	2	2
No	17	80.95	3	2	7	5	9	8

Appendix O- Participants' weekly adherence to oral chemotherapy (percentage) (assessed by Medication Event Monitoring System)

Participants' weekly adherence to oral chemotherapy (percentage) (assessed by Medication Event Monitoring System)



Drug or MEMS use discontinuation (initiated by oncology treating team), A= Adherence (weekly percentage)

Appendix P- Frequencies of symptom presence (with scores ≥3 in the symptom scale) and summed symptom severity scores at baseline and post-intervention (N=21)

Frequencies of symptom presence (with scores ≥3 in the symptom scale) and summed symptom severity scores at baseline and post-intervention (N=21)

	Symptom presence		Symptom severity	
	Baseline (n)	Post-intervention (n)	Baseline (summed score)	Post-intervention (summed score)
diarrhoea	3	3	24	25
nausea/vomiting	2	2	9	12
fatigue	**9**	**15**	**42**	**55**
cough	1	4	11	18
constipation	3	3	17	15
weakness	5	6	**30**	**33**
lack of appetite	4	5	19	26
fever	0	0	3	6
pain	4	7	19	30
hand-foot syndrome	3	6	14	25
mouth sores	3	1	14	13
dry mouth	**6**	**9**	**27**	**34**
numbness and tingling	4	8	21	32
skin rash/sores	1	3	8	17
shortness of breath	3	4	15	22
taste changes	5	7	26	25
disturbed sleep	**9**	**10**	**41**	**41**