Benefits of remote real-time side-effect monitoring systems for patients receiving cancer treatment

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Abstract

In Australia, the incidence of cancer diagnoses is rising along with an aging population. Cancer treatments, such as chemotherapy, are increasingly being provided in the ambulatory care setting. Cancer treatments are commonly associated with distressing and serious side-effects and patients often struggle to manage these themselves without specialized real-time support. Unlike chronic disease populations, few systems for the remote real-time monitoring of cancer patients have been reported. However, several prototype systems have been developed and have received favorable reports. This review aimed to identify and detail systems that reported statistical analyses of changes in patient clinical outcomes, health care system usage or health economic analy-

ses. Five papers were identified that met these criteria. There was wide variation in the design of the monitoring systems in terms of data input method, clinician alerting and response, groups of patients targeted and clinical outcomes measured. The majority of studies had significant methodological weaknesses. These included no control group comparisons, small sample sizes, poor documentation of clinical interventions or measures of adherence to the monitoring systems. In spite of the limitations, promising results emerged in terms of improved clinical outcomes (*e.g.* pain, depression, fatigue). Health care system usage was assessed in two papers with inconsistent results. No studies included health economic analyses. The diversity in systems described, outcomes measured and methodological issues all limited between-study comparisons. Given the acceptability of remote monitoring and the promising outcomes from the few studies analyzing patient or health care system outcomes, future research is needed to rigorously trial these systems to enable greater patient support and safety in the ambulatory setting.

Introduction

The burden of cancer and treatment

In 2007, over 108,000 new cases of cancer were diagnosed in Australia. One in 2 Australians are diagnosed by the age of 85.[1] Cancer care is increasingly being provided in the ambulatory care setting with patients commonly receiving chemotherapy and radiotherapy on an outpatient basis. Chemotherapy is a core treatment for cancer. However, related toxicity can often lead to distressing and even potentially life threatening side-effects (*e.g.* nausea, vomiting, mucositis, diarrhea and febrile neutropenia).[2-11] While some side-effects, such as fatigue and mucositis, are not in themselves life threatening, they are associated with poorer treatment compliance, impaired quality of life, and increased infections and time spent in hospital.[12-14] Fatigue also has a significant impact on patient quality of life and is associated with mood disturbance.[14] Radiotherapy, a second core treatment for cancer, is also associated with distressing side effects (differing according to the site of individual treatment) which may include fatigue, mucositis, and gastrointestinal dysfunctions including diarrhea.[15-19] Many patients also require surgery for their disease and will often experience significant post-surgical problems, such as pain.[20] In addition to treatment-associated morbidity, many cancer patients are required to deal with the symptom burden related to the disease itself. High symptom burden in patients with cancer is also a significant risk factor for adverse psychological adjustment.[21]

In the ambulatory care setting, patients are required to closely monitor and manage a range of potentially diverse and complicated side-effects, without readily available clinical support. Patients are respon-

sible for making potentially complex decisions about when to contact the treatment team in the event of new, escalating or unexpected side-effects. Given that many cancer treatments are highly distressing and may be immunosuppressive, timely response to side-effects is *vital* to optimize patient management and prevent deterioration. It is, therefore, imperative that strategies are in place to assist patients to manage and monitor their side-effects whilst receiving outpatient cancer treatments.

Benefits of telemedicine in chronic disease

Telemedicine devices that allow for the remote, real-time monitoring of symptoms may be a cost-effective strategy to optimize cancer care in the community. Devices which remotely collect and send data to a monitoring station for interpretation and action by a clinician are increasingly being used in the management of chronic diseases, such as diabetes, asthma, heart failure, chronic obstructive pulmonary disease and chronic wound management.[22-27] Research has shown that remote monitoring systems in chronic diseases can lead to improved patient quality of life, symptom control and wound healing rates, reduced lower limb amputations, decreased emergency room visits and unplanned hospitalizations, fewer bed days of care, decreased nursing home admissions in the elderly and decreased overall costs to the health system.[26-29] It is likely that such systems could potentially benefit cancer patients undergoing active treatment in the ambulatory setting, as previous research utilizing submission of daily pen-and-paper measures (linked to defined nursing response algorithms) in chemotherapy patients resulted in significant improvements in side-effects such as nausea and vomiting.[30] The ability to monitor chemotherapy patients at a distance in real-time via remote electronic devices should, therefore, also provide patient and health system benefits.

Prototype remote side-effect monitoring systems for patients with cancer

The earliest reported remote monitoring system used a touch-pad landline phone connected to a computer controlled digitized speech program.[31] Patients called into the system daily and spoke to the system by pressing keys or talking into the receiver. The prevalence of eight key chemotherapy symptoms was reported alongside more detailed information, such as fluid intake and use of medications. Pre-set response thresholds enabled clinicians to be automatically faxed and action taken when patient responses exceeded these limits. Patient compliance with system usage was 75% with the majority of patients expressing satisfaction, finding it easy to use and finding the system increased awareness of side-effects and patterns over time. However, patients noted that the system needed to include additional symptoms for monitoring.

A group of studies by Lind *et al.* report on the first use of mobile phone technology to transmit data from a Bluetooth digital pen/digital paper pain diary.[32-34] This system aimed to improve pain control in palliative cancer patients and also kept record of the pain medications taken. Patients completed diary entries three times a day and alerts of increases in pain were transmitted to the treatment team where they were printed and action was taken by a doctor or nurse. Initially, clinicians had low expectations of the system and the ability of patients to use it and struggled with changing their usual clinical practices. However, clinicians subsequently reported an increased awareness of patient pain and increased patient participation in their care.[33] While patients initially had some difficulty understanding the technology, they reported that it was generally easy to use, that it improved contact with the clinical team and that it made them feel more secure.[34]

Another prototype system that used personal digital assistants for real-time remote monitoring of cancer patients was known as the handheld management system.[35] This system was developed for patients with lung and colorectal cancers undergoing chemotherapy. Patients were asked to answer five symptom questions a day with high scores alerting nurses via a pager system to contact patients via phone. The system also provided tailored self-care messages to patients who reported experiencing symptoms as well as general cancer and treatment information. Study interview data from patients and nurses indicated that the system was easy to use, had the potential to improve symptom management and communication, provided reassurance and support, promoted early detection, and did not disrupt daily routines. Some technical issues around questionnaire submission may have, however, contributed to sub-optimal patient adherence.

A second system, the Advanced Symptom Management System (ASyMS©) has several different versions for patients with cancer undergoing chemotherapy, receiving palliative treatment or for adolescents undergoing chemotherapy.[36-42] ASyMS© uses Smart Phone technology to measure patient temperature and common treatment side-effects twice daily. Alerts are generated when patient questionnaire responses exceed pre-set levels. Alerts are received by a dedicated pager system and classified as either red for urgent action (relating to potentially life-threatening events) or as amber where non-urgent clinical intervention was required. Nurses responding to alerts access a secure website to view patient data reports and then contact patients to provide clinical intervention. Patient devices also provide self-care information to assist in side-effect management based upon reported symptoms, in addition to cancer and treatment information and historical side-effect profiles. Patient and nurse interviews in these studies reported that the system was easy to use,[32-38] enhanced communication,[35,37] increased patient reassurance and support,[33,35,37,38] promoted patient understanding of treatment,[37,38] assisted with symptom management,[32-34,36] and promoted timely intervention.[33,34,37]

Weaver *et al.*[43] also developed a mobile phone based system for patients with colon cancer receiving chemotherapy. This system also focused on temperature and common chemotherapy side-effects, and was linked to a red/amber pager alerting system alongside self-care information and historical side effect profiles. Interviews following use of this system indicated that patients and nurses were confident of using it and that patients felt less bothersome to nurses and more reassured. Two further studies[44,45] have employed a device known as a *Health Buddy* to remotely monitor side effects in head and neck cancer patients undergoing either chemotherapy, radiotherapy or surgery. Patients answered questions daily (the number and type of questions differed with the treatment received) via a landline phone. Patients were provided with self-care advice and instructions on what they should do according to the symptoms reported. This system did not generate alerts, but rather clinicians viewed patient data daily and only contacted patients if symptoms or side-effects were escalating or unresolved. In line with other cancer remote monitoring systems, patients reported feeling reassured, more satisfied with communication and thought they had better knowledge, understanding and management of their symptoms. Patient compliance with completing questionnaires was high in both studies at 84% and 86%; this was unrelated to demographic variables but positively correlated with patient quality of life.

While the initial perceptions of using remote monitoring systems in cancer have been positive, it is still imperative to understand whether the use of such systems positively and significantly impact on *both* patient clinical outcomes, healthcare system usage and health system costs. This review aimed to identify and evaluate studies which quantified changes in patient outcomes and/or health care system usage and costs following the implementation of remote side-effect monitoring systems for patients with cancer undergoing treatment in the ambulatory care setting.

Materials and Methods

Selection process

Studies assessing and quantifying the outcomes of remote monitoring systems in cancer were identified by searching the literature from the period January 2000 and June 2011. The electronic databases Medline, INAHL and PsycINFO and EMBASE were searched. The following search terms were used: cancer OR (*MH Neoplasms*) AND *phone* OR (*MH cellular phone*) OR *telecommunications* OR (*MH Telecommunications) OR* remote monitoring OR *telehealth* OR (*MH Telemedicine*) AND care OR (*MH Ambulatory Care*). In addition, we hand-searched Telemedicine and e-HEALTH and the Journal of Telemedicine and Telecare for articles not retrieved by our search strategy. Reference lists of articles retrieved were also hand-searched.

Inclusion criteria were studies that: i) remotely monitored cancer treatment side effects (*i.e.* in the ambulatory care setting) with the aid of a technological interface (*e.g.* computer; mobile phone); and ii) quantified changes in patient outcomes; or iii) quantified changes in health care system utilization; or iv) quantified changes in health system costs.

Exclusion criteria included studies of: i) phone call or video assessments initiated by a health professional or outreach calls; ii) technology used to capture symptom information immediately before an appointment or on the day of presentation for treatment; iii) centers for patients to call with symptom concerns or need for advice; iv) telemedicine facilities for communication between health professionals (e.g. multidisciplinary meetings at more than one site, second opinions, support for rural practitioners, centralized pathology review); and v) studies reporting only on the development of system prototypes and/or with no statistical analyses of pre-specified patient or health service outcomes/variables.

Study variables

The study variables used for reviewing papers included: country of origin, year of publication, study design, study hypotheses, patient and clinician population, sample size, description of the remote monitoring systems (data collection, alerting systems, clinical responses, duration and frequency of monitoring), patient and clinician adherence to use of the monitoring system, previous publication of the monitoring system, patient clinical and health system usage outcomes, health economic analyses, and any potential sources of bias. In addition the *level of evidence* associated with each study design was categorized using National Health and Medical Research Council of Australia guidelines.[46] These categories reflect the level of bias inherent in different study designs when assessing the effectiveness of health interventions with a lower number (*e.g.* I or II) indicating less bias than a higher number (*e.g.* III or IV).

Analysis

Assessment of studies identified in relation to pre-specified study variables was undertaken independently by three authors (SK, SB and KG). These assessments were then compared and any discrepancies discussed until agreement was reached.

Results

Twenty-five studies that centered on a *real-time* remote symptom monitoring system in cancer patients were identified (Figure 1). Of these, five papers met the inclusion criteria including one case control study,[47] one post test case series[48] and three randomized controlled tri-

als (RCT).[49-51] The systems examined in these studies have the common basis of employing a remote device (such as a Smart Phone or automated interactive telephone calls) to facilitate the generation of alerts when symptoms or side-effects reach a pre-defined threshold of severity. These alerts are then transmitted to a health center for a response. The user interfaces, data gathered, health setting, alerting mechanisms, health professionals and clinical interventions provided also varied widely. Three of the papers[47-49] also reported the automated provision of tailored self-care advice to the patients experiencing side-effects in addition to clinical interventions. A summary of the systems tested is shown in Table 1.

Clinical outcomes

The methodological designs, sample populations and sizes, as well as the outcomes measured, varied considerably and are summarized in Table 2.

Kearney *et al*.[49] found that patients in the intervention group reported less fatigue post chemotherapy in a randomized controlled trial. However, there was no significant difference in reports of vomiting, nausea, diarrhea, sore mouth or throat between the two study arms. The authors also noted an unexplained decrease in prevalence, severity and distress caused by hand-foot syndrome in the control group.

Benefits seen in the intervention group of an RCT by Kroenke et al.[50] included lower severity of pain and greater improvement in depression across the study period. The intervention group also reported greater improvement in some secondary end points, including the Sheehan Disability Scale, individual domains of Health Related Quality of Life (HRQOL) measures, anxiety and physical symptom burden. Differences in self-reported disability days, physical health and overall quality of life were not statistically significant. Interestingly, this study
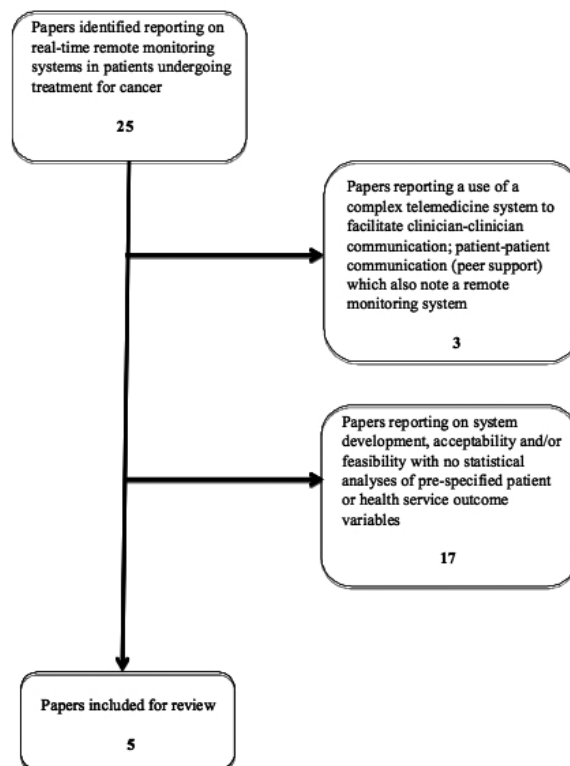

Figure 1. Summary of papers identified and subsequently excluded/included in this review.

Table 1. Description of the remote real-time side-effect monitoring systems.

Authors	Country	Population for whom the system was developed	System description	Patient parameters monitored	Frequency of data completion and transmission	Nature of clinical intervention mediated by technology	Additional system functionality
Chumbler et al. (2007)[47]	USA	Veterans with a new diagnosis of cancer undergoing chemotherapy treatment in the ambulatory setting.	A home messaging service (Health Buddy) is connected to the home landline of the patient. Patients answer questions using the touchpad of their telephone and information is transmitted to a member of the treatment team via an unstated mechanism. The system is set up in the patient home during a home visit by a nurse from the treatment team (Care Coordinator).	Pain, fatigue, nausea, nervousness/worry and functional limitations. Questions were adapted from the MDASI and pre-tested for reliability and validity. Symptom prevalences were assessed as dichotomous variables (1=Yes; 0=No). Daily responses were converted into monthly symptom reports.	Daily	A nurse designated as a Care Coordinator received patient data. How the Care Coordinator responded to patient data is not reported.	Upon completion of the symptom questionnaires, patients received self-care feedback relevant to the symptoms reported.
Chumbler et al. (2007)[48]	USA	Veterans with a newly confirmed diagnosis of cancer undergoing chemotherapy treatment in the ambulatory setting.	An in-home messaging service plugged into a touchpad landline phone supports patients to answer questions about their symptoms (daily cancer care dialogues). Patient data is transmitted via a 1800 phone number to the internet and then to the computer of a Care Coordinator. Any answer that surpassed an agreed upon symptom threshold automatically alerted the Care Coordinator to call the patient.	Pain, fatigue, nausea, functional limitations and emotional distress. No specific details of format or the origin of these questions was reported.	Daily	Symptoms were monitored and responded to by a Care Coordinator who used clinical judgment to resolve the patients' problems such as making a timely clinic referral, reinforcing symptom-based education or offering encouragement and reassurance.	Upon completion of the symptom questionnaires, patients received self-care feedback relevant to the symptoms reported.
Kearney et al. (2009)[49]	UK	Patients with breast, lung or colorectal cancer receiving chemotherapy treatment in an ambulatory care setting.	The ASyMS© system allows patients to report on chemotherapy symptoms via a mobile phone application which transmits data to a secure server. Algorithms within the system categorize data and generate alerts when pre-determined levels of symptoms are exceeded. Alerts are generated to the treatment team via a dedicated pager system. Alerts are categorized into two levels: red for potentially life threatening symptoms and amber for non-life threatening levels of symptomatology that could benefit from early intervention to prevent symptom progression.	Nausea, vomiting, fatigue, mucositis, hand-foot syndrome and diarrhea. Questions ask whether a patient has experienced a symptom (Yes/No) and if Yes, then how severe it was (mild, moderate, severe) and how much it bothered them (not at all, a little, quite a bit, very much). Symptoms were selected following literature reviews of the population and patient/clinician feedback. Questions are based on those from the CSAS a validated chemotherapy side effect, questionnaire. Symptom severity descriptors are based on those used clinically in the CTCAE grading system.	Twice daily	An oncology nurse within the treatment hospital accesses a secure webpage to view individual patient symptom reports and histories that aid clinical decision making. Nurses contact the patient via phone to provide appropriate clinical interventions as required.	Tailored self-care advice provided to patients on the phone following completion of each symptoms questionnaire. Self-care is tailored to both the type and level of symptom experienced. Self-care included simple instructions for patients to manage their symptoms including advice on medicines, use of distraction or meditation techniques and dietary advice as appropriate.

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Table 1. Continued from previous page.

Authors	Country	Population for whom the system was developed	System description	Patient parameters monitored	Frequency of data completion and transmission	Nature of clinical intervention mediated by technology	Additional system functionality
Kroenke et al. 2010[50]	USA	Oncology patients with elevated levels of pain or depression at any point in the disease/treatment trajectory who are in the ambulatory care setting.	Automated symptom monitoring performed using either interactive voice-recorded telephone calls or web-based surveys based on patient preference. Clinical follow up of completed questionnaires was provided in the cases of inadequate symptom control/improvement, non-adherence to medication schedules, suicidal ideation or from a patient request to be contacted. In addition three scheduled follow up calls to patients from the Nurse Care Manager were scheduled at 1, 4 and 12 weeks.	Twenty-one survey items from previously validated measures were included: 8 questions from the BPI of which 3 asked about pain severity and 5 asked about pain interference; and the PHQ-9 depression scale. Patients were also asked single questions about medication adherence, adverse effects, global improvement and whether they wanted a nurse care manager call.	Weeks 1-3: twice weekly Weeks 4-11: weekly Months 3-6: twice a month Months 7-12: once a month	Nurse care manager with training in assessing symptoms, medication adherence, providing pain and depression specific information and treatment adjustments according to pre-determined evidence based algorithms. The Nurse Care Manager meets weekly to review cases with pain-psychiatrist specialist. Medications prescribed as needed by the patient's oncologist	None
Cleeland et al. 2011[51]	USA	Post-thoracotomy oncology patients with lung cancer or lung metastases in the ambulatory care setting.	An automatically generated telephone call to patients, which uses an IVR system, linked to a triage alerting system. Should patient responses exceed pre-set limits (as determined by the opinions of thoracic surgery clinicians) then an e-mail alert to the treatment team is generated.	Pain, distress, disturbed sleep, shortness of breath plus constipation. Items were selected based upon previous survey data indicating the most severe post-surgical symptoms that were considered to be manageable via phone consultation. Five items in total were adapted from the validated MDASI questionnaire of common cancer related symptoms.	Twice weekly	The surgical team's advanced practice nurse would read e-mails and contact the patient as appropriate. Nursing actions recorded via return e-mail.	None

MDASI, MD Anderson Symptom Inventory; ASyMS, Advanced Symptom; Management System; CSAS, Chemotherapy Symptom Assessment Scale; CTCAE, Common Toxicity Criteria Adverse Events; BPI, Brief Pain Inventory; PHQ, Patient Health Questionnaire; IVR, Interactive Voice Response.

Table 2. Study designs and results.

Authors	Study design and level of evidence[46]	Study setting and sample	Study aims and/ or hypotheses	Sample size	Sample characteristics	Study participation	Outcomes
Chumbler et al.[47]	Post-test case series/clinical follow up (Level IV)	Veterans from a single Veterans Affairs Medical center newly diagnosed with cancer and scheduled to receive chemotherapy (including lung, colorectal, head and neck and *other* undefined primary cancer sites).	Aims: to test the feasibility of the remote monitoring *Cancer Dialogue* system. Hypotheses: i) patients will maintain a high level of cooperation despite remote nature of the system; ii) patient cooperation with the dialogue system and better symptom management will be associated with stable or improved HRQOL during chemotherapy treatment.	34 patients	Mean age=64 yrs 94% male Lung 35% Head & Neck 24% Colorectal 21% Other site 21% Stage I/II 9% Stage III 47% Stage IV 44%	6 months OR for duration of chemotherapy OR until study concluded.	- Patient compliance decreased over the course of the study from 87.3 to 80.9. - However, there was a high level of overall compliance with using the system (84%). - Adjusting for clinical factors, patient HRQOL significantly increased 6.45 points (a clinically meaningful difference). - Patient nervousness/worry and end of treatment time were significant predictors of HRQOL (no P values provided). - Age was also associated with patient HRQOL.
Chumbler et al.[48]	Case-control (Level III-2)	Veterans from a single VA medical center newly diagnosed with cancer and scheduled to receive chemotherapy (including lung, colorectal, head and neck and other undefined primary cancer sites)	Aims: to compare the use of VA inpatient and outpatient preventable (unplanned) service use and cancer related service use (planned). Hypotheses: i) intervention group patients will use fewer preventable services than standard VA care; ii) intervention group patients will use more planned cancer-related services.	Intervention group: 43 Control group: 82 Controls case-matched to intervention group based on cancer type and cancer stage. Control group patients did not use the monitoring system and received *standard VA care*.	Intervention group: Mean age=64 yrs Male 95% Lung 48% Head & Neck 19% Colorectal 19% Other 15% Stage III 38% Stage IV 48% Control group: Mean age=63 yr Male 94% Lung 53% Head & Neck 159% Colorectal 18% Other 13% Stage I/II 12% Stage III 27% Stage IV 61%	6 months	*Preventable service utilization.* Intervention patients had: - fewer clinic visits ($P<0.01$); - fewer BDOC (all causes) ($P<0.01$) - fewer BDOC (chemotherapy related causes) ($P<0.05$) - fewer chemotherapy BDOC ($P<0.01$) *Cancer-related service utilization* Intervention patients had: - fewer clinic visits ($P<0.01$) - more cancer-related chemotherapy hospitalizations ($P<0.05$).
Kearney et al.[49]	RCT (Level II)	Patients with a diagnosis of breast, lung or colorectal cancer receiving a new course of chemotherapy at one of seven hospitals across the United Kingdom (6 in Scotland; 1 England). Five hospitals were specialist cancer centers and 2 were local district hospitals.	Aims: to investigate the viability of the trial design and explore any effect of the ASyMS© system on the incidence, severity and distress caused by 6 chemotherapy-related symptoms. Hypotheses: i) the ASyMS© mobile phone system would provide a more accurate reflection of chemotherapy toxicities; ii) the ASyMS© system would provide a better means of monitoring chemotherapy-related toxicity.	Intervention group: 56 (29 participated in study for all 4 cycles of chemotherapy) Control group: 56 (29 participated in study for all 4 cycles of chemotherapy)	Mean age=56 yr Male 23% Breast 63% Lung 23% Colorectal 14.3% No staging information collected.	Duration of 4 cycles of chemotherapy Intervention group patients completed the ASyMS mobile phone questionnaires on days 1-14 of each chemotherapy cycle.	- Lower incidence of fatigue in the intervention group ($P<0.05$) - Trend towards decreased distress due to fatigue in the intervention group ($P=0.08$) - Lower incidence of hand-foot syndrome in the control group ($P<0.05$) - Lower levels of severity and distress associated with hand-foot syndrome in the control group ($P<0.05$)

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Table 2. Continued from previous page.

Authors	Study design and level of evidence[46]	Study setting and sample	Study aims and/or hypotheses	Sample size	Sample characteristics	Study participation	Outcomes
Kroenke et al.[50]	RCT (Level II)	Oncology patients with breast, lung, gastrointestinal, lymphoma, hematologic, genitourinary and *other* undefined tumors with elevated levels of pain and/or depression. Recruitment from 16 community-based urban and rural oncology cancer practices.	Aim: to trial a collaborative care approach to managing depression and pain in geographically dispersed oncology practices state-wide (*i.e.* centralized care management combined with automated disease monitoring facilitated coverage of multiple urban and rural oncology practices). Hypothesis: the telecare management intervention would be superior to *usual care* in improving patient outcomes of pain and depression.	Intervention group: 202 (134 still enrolled at 12 months) Control group: 203 (135 still enrolled at 12 months) Control group patients received *usual care* for their cancer at each of the16 recruitment sites	*Intervention group* Mean age=59 yrs Male 37% Breast 27% Lung 21% Gastrointestinal 20% Lymphoma/Hem 11% Genitourinary 8% Other 13 Newly diagnosed 37% Maintenance/disease free 39% Recurrent/progressive 25% Control group Mean age=59 yrs Male 28% Breast 31% Lung 19% Gastrointestinal 15% Lymphoma/Hem 15% Genitourinary 12% Other 8 Newly diagnosed 37% Maintenance/disease free 46% Recurrent/progressive 16%	12 months	Intervention group patients had significantly greater: - improvements in pain over the 12 months (P<0.01) and at all other study time points (P<0.01) with an effect size of 0.36-0.67 - improvements in pain interference scores (P<0.001) - improvements in overall bodily pain scores (P<0.01) - improvements in depression measured as a continuous variable at 12 months (P<0.001) and at all other time points (P<0.01) with effect sizes ranging from 0.31-0.45 - improvements in severity of depression at 12 months (P<0.01) - fewer major depressive disorders at 12 months (P<0.001) - improvements in QOL subscales including vitality (P<0.05) and mental health (P<0.05) - decreased anxiety (P<0.01) - decreased physical symptom burden (P<0.05) - improvements on the Sheehan Disability Scale (P<0.05) There were no significant differences between groups for: - health related quality of life - hospital BDOC - Emergency Department visits - self-reported disability days - self-reported use of potential co-interventions

Table 2. Continued from previous page.

Authors	Study design and level of evidence[46]	Study setting and sample	Study aims and/ or hypotheses	Sample size	Sample characteristics	Study participation	Outcomes
Cleeland *et al.*[51]	RCT (Level II)	Patients post-thoracotomy for lung cancer or lung metastases following discharge from hospital (*i.e.* in the ambulatory care setting). Recruitment was from one tertiary cancer care center focusing on symptom control.	Aims: to test an IVR triage alert system in patients undergoing thoracotomy for lung cancer or lung metastases. Hypotheses: i) patients in the intervention group are less likely to have symptoms that meet or exceed pre-determined severity thresholds; ii) patients in the intervention group would have lower symptom interference and higher acceptability of the IVR assessment system and satisfaction with symptom control.	Intervention group: 38 patients Control group: 41 patients Control group patients also symptoms questionnaires but received *usual care* for their symptoms (*i.e.* data was not responded to by the advanced practice nurse in real-time).	Intervention group Mean age 59 years Male 55% Lung non-small cell 42 Colon/rectum 13 Sarcoma 26.3 Melanoma 8 Kidney 5.3 Esophagus 3 Other 3 Stage I 21 Stage II 6 Stage III 24 Stage IV 50 Control group Mean age 61 years Male 51% Lung small cell 5 Lung non-small cell 49 Colon/rectum 15 Sarcoma 15 Melanoma 5 Kidney 5 Head & Neck 5 Uterus 2 Stage I 29 Stage II 14 Stage III 9 Stage IV+ 49	4 weeks post thoracotomy	- All patients reported a reduction in symptom threshold events over time with an average reduction of 19% in the intervention group and 8% in the control group. - Intervention patients reported a more rapid decline in events than usual care group patients (P=0.003). - There was no significant difference in the severity of symptoms. - Intervention patients had significantly lower mean symptom interference scores (P<0.02) with an effect size over time of 0.36. - Intervention patients were more comfortable with using the IVR system (P<0.03) and were more likely to rate it as easy to use (P<0.01).

HRQOL, Health Related Quality of Life; BDOC, bed days of care; VA, Veterans Affairs; IVR, Interactive Voice Response; Hem, haematological.

Table 3. Study strengths and weaknesses.

Authors	Study strengths	Study weaknesses
Chumbler et al.[47]	- Symptom data collection questions based on reliable and valid cancer specific instruments - System contained both psychological as well as physical symptom variables - System provided tailored self-care advice to patients reporting symptoms - Alert levels of symptoms pre-defined - Monthly symptom reports available for clinicians - Patient compliance with system use measured and reported - Outcome measures are reliable and valid - Published pilot work on system development	- Level IV evidence with no control comparisons/pre-test data available - Small sample size limited analyses - Changes in HRQOL over time could be due to response shift and not the remote monitoring system - *Treatment time* as a predictor of HRQOL not defined - Potential selection biases or questions of limited generalizability to a broader patient group given it included: only veterans from one cancer center; 94% male; 91% late stage disease - No measures of nursing compliance or time taken to provide interventions - No reporting of the clinical response to patients in need or as to whether standardized algorithms/protocols were used to structure the nursing response - Did not fully test hypotheses presented with no comparisons of improvements in HRQOL between compliant and non-compliant patients - No service use data or health economic analyses reported
Chumbler et al.[48]	- Level III-2 study design - Patients were matched similarly along key characteristics that would determine chemotherapy and other therapies - Alert levels of symptoms pre-defined - System contained both psychological as well as physical symptom variables - System provided tailored evidence-based self-care advice to patients reporting symptoms - Detailed pre-set definitions of planned/expected visits *versus* unplanned visits for patients in the study in terms of resource usage of patients at treatment site - Published pilot work on system development	- As a non-randomized study, inadvertent confounders may have attributed to study findings - Unclear how intervention patients were chosen to participate in the study - Potential selection biases or questions of limited generalizability to a broader patient group given it included: only veterans from one cancer center; 94% male; receiving chemotherapy for the first time; 85% with late stage disease - No case-matching to age, gender, co-morbidities or symptom severity or types of cancer other than lung, head & neck or colorectal - No standardized nursing response algorithms reported - Length and content of nurse calls not reported - Mechanism of alerting care coordinator is not clear - No measures of either patient or care coordinator compliance with using the system/responding to patient symptoms - No usage of non-treatment hospital resources reported (*e.g.* GPs, allied health etc.) - No definition of standard VA care given or clarification of control patient calls reported to the *telecare* system - No economic analysis or assessment of potential cost savings
Kearney et al.[49]	- Level II study design - ASyMS© symptom questionnaire based on validated tools developed for cancer patients having chemotherapy - Published pilot work on the development of the system - Pre-defined alerting algorithms - System provided tailored evidence-based self-care advice to patients reporting symptoms - Multi-site study with both cancer specialist hospitals and local district sites included - Broadly applicable patient group including three major cancer sites	- Underpowered to detect clinically important differences in outcome measures - The same questions used for the remote symptom reporting and the outcome measures may have led to greater familiarity in intervention patients than control group patients - Potential selection bias in relation to 77% of the sample being female - No reported standardized nursing intervention algorithms to respond to patient alerts - No patient compliance with the monitoring system reported - No nursing compliance with the monitoring system reported - High attrition rate - No HRQOL or psychological variables monitored - No measurement of patient use of self-care advice - No consent rate data reported - No primary end point reported - No economic analysis or use of hospital resources reported - No usage of non-treatment hospital resources reported (*e.g.* GPs, allied health etc.)

Table 3. Continued from previous page.

Authors	Study strengths	Study weaknesses
Kroenke *et al.*[50]	- Level II study design - Validated tools used in the automated symptom survey - Psychological and physical issues monitored - Clinically significant clinically meaningful end points were pre-determined - Pre-determined response algorithms that were evidence-based were used to guide nursing response - Recruitment from 16 separate sites state-wide - Calls about difficult/troublesome symptoms combined with schedule nurse follow-up calls - Focus on highly prevalent cancer symptoms of pain and depression - Previously published details of clinical response algorithms - Demonstrated clear impact on primary end points - Clinically meaningful effect demonstrated in the intervention group (not just a difference on a continuous scale) - Documentation of nursing time utilized in intervention arm	- No stratification by cancer site or by method of monitoring (phone *vs* internet) - No details provided of scheduled calls by nurses - Potential bias of 68% female sample - Large numbers of ineligible patients may indicate lower generalizability of the system - No patient or nursing intervention adherence data reported - Less complete assessment of outcome measures in the control group - The patient was asked if the doctor thought that the pain was related to their cancer but the answer was not validated by chart review or oncologist verification - No documentation of nursing for control group patients - No economic analysis or reporting on health care system usage
Cleeland *et al.*[51]	- Level II study design - Robust differences in outcome measures despite not reaching required sample size - Pre-defined symptom alerting criteria - Symptoms monitored based on prevalence/severity from a previous study and expert opinion - Nursing intervention compliance reported	- Underpowered and sample size did not allow for statistical analyses of individual symptom improvements - Control group not receiving true *usual care* as they completed the automated assessment (but it was not linked to the threshold incident system) - No response algorithms reported to standardize nursing clinical response - Limited genereralizability in relation to recruitment from only one site (a specialist cancer center) and only a post thoracotomy surgery population - Issues with nursing intervention compliance (only 84% thresholds responded to and 60% of calls made) - No reporting on appropriateness of nursing interventions provided - Only choice to notify nurses over symptoms that clinical team felt that *something could be done about via telephone* - No economic analyses or reporting on health care system usage

HRQOL, Health Related Quality of Life; VA, Veterans Affairs; ASyMS, Advanced Symptom Management System; GP, General Practitioners.

also had additional scheduled remote patient follow up by clinicians in addition to responding to remotely reported patient symptoms.

Cleeland et al.[51] found that in their RCT of post-thoracotomy patients the intervention group had a significantly greater reduction in post-operative symptom threshold events; these had been pre-defined in consultation with thoracic surgery staff. The intervention group also saw a more rapid decline in numbers of events and had less interference with their activities of daily living. There were no statistically significant differences in self-reported severity of symptoms between the two study arms; however, the study was underpowered.

The post test case series performed by Chumbler et al.[48] studied the effect on HRQOL in 34 patients utilising a home telehealth program. They demonstrated that HRQL in this small population increased over a 6-month period. In the absence of a control group comparison, the possibility that this was due to response shift or another confounding variable cannot be ruled out.

Healthcare system outcomes

Only two papers reported on health care system outcomes. Building on their post test case series, Chumbler et al.[47] performed a matched case-control study examining the impact of a remote symptom monitoring system on healthcare use among veterans undergoing chemotherapy. They demonstrated a decrease in the use of a number of preventable services but did not perform an economic analysis. In their study, Kroenke et al.[50] did not observe any statistically significant difference in hospital days and emergency department visits between their two groups. No study performed any cost-benefit or other health economic analyses. This is possibly related to limitations in the medical record whereby all variables required to complete these complex assessments may not have been consistently registered.

Study strengths and limitations

A summary of the strengths and limitations is provided in Table 3. Comparisons of results between studies were limited by differences in design, outcomes measured, monitoring systems and methodologies used. Study limitations included small sample sizes (underpowered analyses), participant selection bias, population generalizability and low levels of evidence linked to study design.[46] However, despite the limitations, significant differences were observed in RCTs and the improvements and changes reported in patients were generally robust.

Discussion

To date there have been few studies in the cancer population of the impact of telecommunication-based devices that regularly collect data from patients at home and transmit the results to a healthcare professional for response in real-time. Given the distressing and serious side-effects that are common during and following cancer treatments[2-21] this is surprising given the apparent cost-effectiveness of these systems in chronic disease patients. This review aimed to identify papers that not only described remote monitoring systems in cancer patients, but also statistically analyzed patient clinical and health care system outcomes. Only five published trials were found, of which three were RCTs and of these only one was sufficiently powered. No studies were completed within the context of the Australian health care system.

The majority of the studies had several methodological limitations which include using the same questionnaire for the intervention and outcome measure,[49] heterogeneous populations precluding more precise estimates of treatment effect in specific types or stages of cancer,[47-50] less complete assessment of outcome measures in the control

group,[50] eligibility criteria requiring the presence of the symptom at trial commencement[50] and the control group using the automated system without response such that the control group was in effect no longer receiving usual care.[51] These limitations together with the differences in remote monitoring systems and patient populations reduced our ability to generalize or confirm the findings of previous trials and to make cross-study comparisons. Essentially, the available RCTs have examined three separate complex interventions and it is practically impossible to make a comparison between them. It is also difficult to know whether changes in patient and health system outcomes are due to the symptoms monitored, the frequency of monitoring, the technological interface, the person and/or algorithms guiding responses to the alerts, or whether or not automatic self-care advice is given.

Despite the limitations, there have been some promising results to guide future research. Of note, the adequately powered study by Kroenke et al.[50] demonstrated clinically significant intervention effects on the primary end points (pain and depression) as well as other secondary outcomes. It must be remembered, however, that this study was conducted in patients with pre-existing pain or depression so the results may not be generalized to those without a pre-existing condition. Although the study by Cleeland et al.[51] was underpowered, it did demonstrate large between-group differences in post-thoracotomy symptom threshold events overall, and larger future studies may be able to identify differences within individual symptoms and severity. Remote symptom monitoring systems may reduce fatigue post chemotherapy.[49] Fatigue is a common and often overlooked side-effect which is difficult to manage and is linked with poor HRQOL and mood disturbance.

It is interesting that while reassurance was a key theme that emerged from the previous qualitative studies, none of the RCTs in this review included anxiety as a primary outcome measure. Kearney et al.[49] did examine the distress associated with each of the side-effects and the differences between the two groups; however, they did not include a measure of overall anxiety. The study by Kroenke et al.[50] was the only study to measure anxiety as a secondary outcome and found that it was significantly reduced in the intervention monitoring group. Alongside improvements in depression, this suggests that remote monitoring shows promise for improving patient psychological as well as physical outcomes.

Despite the fact that patients were monitored less often and were not provided with automated self-care advice, the results from the study by Kroenke et al.[50] are the most convincing evidence for the effectiveness of remote monitoring in a wide-variety of cancer patients. This system differs from the others in that a team of people (nurse, psychiatrist and oncologist) are involved in the management of the symptoms reported in a structured and consistent manner, rather than the responsibility falling on one person. This may have influenced the quality of the intervention and hence the outcome of the trial. In addition, interventions were guided by previously published evidence-based clinical algorithms (including pharmacotherapy) that were not reported in the other studies. This system and associated intervention also differed from all of the others in that scheduled remote follow ups with patients were completed in addition to responding ad hoc to problematic symptoms. The contribution that this may have made to the overall study results is unclear. The success of this study may just be that it is easier to show improvements in pre-existing symptoms when compared with aiming to prevent symptoms or future side-effects.

No study clearly documented both nurse and patient adherence to the use of the remote monitoring systems or reported on the appropriateness of actions taken or whether they were consistent with any pre-defined clinical response algorithms. Those systems providing patients with self-care advice were also unable to report on the frequency of

patient access to this information, or more importantly, whether the patients used the information provided. Cleeland et al.[51] reported that only a subset of threshold events triggered clinician responses which may have also affected study outcomes. Kearney et al.[49] provided very little information about clinical interventions instituted in response to alerts so it is difficult to tell whether or not they were consistent across the study and between study sites.

Although not randomized, the case-control study by Chumbler et al.[48] demonstrated promising benefits to the healthcare system in terms of unplanned presentations and bed days of care. Given that the introduction of a new technology has a price attached to it, there is a need to establish that this cost is offset by the clinical impact of using these devices. No health economic analyses of remote real-time monitoring devices in cancer were identified in the peer-reviewed literature. These studies are necessary if there is to be widespread uptake of this type of technology as healthcare administrators are unlikely to fund an intervention that does not have economic benefit. It is important to remember that technology such as remote monitoring does not replace face-to-face patient contact but complements it. As such, there are costs associated with the provision of the technology for patient use, data transfer charges and time taken for the health professional to monitor and respond to such systems. Whether these then decrease health care system costs across the board is a broader issue. Not only is it important to measure inpatient and outpatient costs and health care system usage, it is also necessary to consider other costs that may be incurred by the patient from the implementation of these models of care, for example, visits to general practitioners or other community health services. Newer technology being developed may also mean that additional parameters could be measured in the ambulatory care setting when needed (e.g. blood tests) and the costs of devices to allow this also need to be factored into future cost analyses.

All of the studies included in this review have been published in the past five years which suggests that this is an emerging facet of cancer care. However, in addition to the completion of more rigorous studies to fully assess cost-effectiveness of such remote monitoring systems, health services also need to think about how such care provision can be funded given the limitations of current systems. It is also possible that such remote monitoring will not prove cost-effective for all patients undergoing treatment. The successful study of Kroenke et al.[50] only looked at patients who already had significant clinical issues. It is, therefore, possible that such systems may only be cost-effective for those cancer patients who are at high risk of adverse outcomes due to high toxicity treatments (e.g. hematological cancer patients), already symptomatic or who have significant co-morbidities. Future research should also focus on these groups when considering cost-benefits of remote monitoring systems.

Conclusions and future directions

There are very few studies examining the outcomes of real-time remote symptom monitoring devices in patients with cancer. There is some evidence that they can reduce morbidity and prevent unplanned hospitalizations. However, results are mixed. It is very difficult to make generalizations given that there is no consistency in the monitoring devices used, disease type, treatments, side-effects or symptoms monitored, and breadth of management and interventions. More sufficiently powered randomized control trials, which also assess adherence to the intervention and include a full economic analysis, are warranted. A full examination of these benefits is a key priority within the Australian health care system alongside an exploration of health care funding models to support their implementation. With the aging of the population, and the resultant increase in cancer diagnoses, it is vital to explore systems to provide ambulatory care in a safer and more economically viable manner as well as to potentially target high-risk groups who would benefit most from such interventions.

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