Real-time management of chemotherapy toxicity using the Advanced Symptom Management System (ASyMS)

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Real-time management of chemotherapy toxicity using the Advanced Symptom Management System (ASyMS)

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This paper describes an ongoing study of the Advanced Symptom Management System (ASyMS) for patients receiving chemotherapy for breast or colorectal cancer. We begin by detailing the ASyMS work to date, providing an overview of research conducted in the field over the last ten years. The current study, ASyMS-III, is then presented, highlighting the study methodology, multi-site involvement, the outcomes being measured, and discussion of the tool. The paper concludes with reflections on the progress of the ASyMS-III study to date, and discusses potential directions for future research.

Keywords: real-time symptom assessment; smartphone technology; chemotherapy related toxicities

1. Background

In Scotland alone, in 2009, 29,500 new cases of cancer were diagnosed. Whilst lung cancer continues to be the most common cancer overall in Scotland (17% of all cancers), breast and colorectal cancers are also commonly diagnosed, with 15% and 13% of cases diagnosed respectively in 2009 (Information Services Division, 2010). A core treatment modality in the treatment of these cancers is chemotherapy, in which cytotoxic drugs are administered to destroy the cancer cells (Macmillan Cancer Support, 2012). The toxicities from chemotherapy treatments can often lead to distressing and potentially life-threatening side effects for patients (Butt et al., 2008; Du et al., 2002; Kuderer et al., 2006; Park & Trovato, 2004; Richardson & Ream, 1996). Such side effects have previously been reported to be associated with poor treatment adherence, impaired quality of life, increased infections and increased time spent in hospital (Kuderer et al., 2006; Murphy 2007).

Chemotherapy is traditionally delivered in day-treatment units or in-patient settings. Following treatment, patients are frequently discharged into the community and are thus responsible for monitoring any side effects at home. However, there may be hesitance or reluctance on the part of the patient to inform their treatment team of problematic symptoms or side effects, fearing this may result in hospitalisation (Saunders, 2008). Whilst structured symptom assessment tools and the implementation of timely management strategies have demonstrated improvements in patients’ physical and emotional outcomes (Boyes et al., 2006; Macvean et al., 2007), all too often tools such as these rely on retrospective patient recall to allow...
completion. Such recall is consequently prone to recall bias (Litt et al., 1998) and associated delays can impede a timely clinical response. Therefore, the ability to capture symptom data in ‘real time’ is now regarded as the gold standard to allow rapid clinical decision-making and intervention to improve patient outcomes.

2. Trends in health care provision

In current health care provision, there is a shift of balance and process of care occurring from hospital-based care to community-based models. Whilst this is welcomed by patients and seen to benefit local health systems, it may be a barrier to the delivery of effective symptom management. Care delivered as an outpatient results in patients having to manage the majority of the associated side effects at home without direct supervision from health care personnel. This may mean some patients re-contact health services seeking reassurance or, worse, do not recognise potentially serious symptoms and do not seek help.

In the context of chemotherapy, the shift of chemotherapy administration into the ambulatory environment requires the patient to engage in self-care activities to prevent or reduce the severity of numerous and possibly complex side effects. In addition, patients often report the need ‘to be informed about the things you can do to help yourself get well’ (Chumbler et al., 2005). Development of patient self-care is critically important to ensure safe and high quality care at home. Self-care interventions in patients with cancer have been reported to reduce psychological distress, reduce patient concerns about treatment, decrease barriers to self-care and improve symptoms (Louis et al., 2003; Rasmussen et al., 2005). Despite positive outcomes, these interventions are hampered by the inability to respond to patients concerns in ‘real time’. Furthermore systematic reviews in cancer and other chronic conditions conclude that research, in particular intervention studies, are a priority to guide practice to improve patient and family self-management (Chumbler et al., 2007a; Chumbler et al., 2007b).

3. Telehealth and telecare

As highlighted previously, there is a paradigm shift in the way health services are delivered across the UK. As a result of UK health policy, there is an increasing number of individuals receiving care within a community setting (Department of Health, 2007; Scottish Government, 2007). Innovative technology systems may be seen as a way to support this shift in working patterns. Telehealth and telecare systems are being harnessed across the county, and there is increasing interest in how such systems can support an individual’s health needs in the community (Scottish Government, 2007). Such telehealth and telecare systems are seen to facilitate the provision of clear lines of real-time communication between patients and their health care providers. In addition, many of these technologies are patient centred, and are seen to compliment the current transitions within health care, shifting care from the acute hospital setting to the home environment, while maintaining patient safety and delivering effective monitoring.

Telehealth monitoring is the real-time remote exchange of physiological or symptom data between patients in the community and clinicians in a treatment facility. Telehealth systems commonly utilise the Internet, phone lines (land or mobile), video links or combinations of these systems. To date, technology has enabled successful assessment of symptoms in patients with chronic diseases such as diabetes, heart failure, chronic obstructive airways disease, and chronic wound management (Barnett et al., 2006; Chumbler et al., 2005; Louis et al., 2003; Rasmussen et al., 2005; West, 2012). Examples of how the technology has impacted care include improved quality of life, symptom burden, and wound healing rates, reduced lower
limb amputations, decreased emergency room visits and unplanned hospitalisations, fewer bed
days of care, decreased nursing home admissions in the elderly, decreased overall costs to the
health system and promoting positive behavioural change (Bartoli et al., 2009; Black et al.,
2011; Cleland et al., 2005; Cueva, 2010). Despite these successes, there exists a paucity of
appropriate telehealth systems for patients with cancer (Chumbler et al., 2007a, 2007b; Kear-
ney et al., 2009; Kearney et al., 2006), even though there is empirical evidence which sub-
stantiates their role in the delivery of supportive care to people living with the complexities
of chronic health conditions.

4. The Advanced Symptom Management System (ASyMS)

In response to two predominant issues raised above – the need to capture real-time informa-
tion to allow timely clinical interventions and the scarcity but applicability of such technology
within a cancer care context (Gibson et al., 2010; Kearney et al., 2006, 2009; Maguire et al.,
2005, 2008a, 2008b; McCall et al., 2008; McCann et al., 2009), Kearney and colleagues have
developed and evolved a system over recent years to facilitate the remote monitoring and
management of chemotherapy-related toxicity in patients. The mobile phone-based Advanced
Symptom Management System (ASyMS) intervention has a number of core principles:

1. Patients participating in an ASyMS research study are provided with a pre-pro-
grammed mobile phone.

2. Using the mobile phone twice daily, and at any other time they feel unwell, patients
complete a symptom questionnaire and record their temperature on the device. This
information is then sent in ‘real time’ to the secure study server, triggering two subse-
quent simultaneous actions. Firstly, patients are provided with evidence-based self-care
advice directly on the mobile phone to help manage their symptoms. Secondly, upon
receipt of the symptom information, an inbuilt risk modelling algorithm generates a
triaged level of alert to the appropriate clinical site for any symptoms of clinical con-
cern reported by the patient. The designated cancer specialist at the clinical site then
immediately receives an alert on a mobile device and web-based system, allowing
intervention according to local policies and procedures.

3. Two levels of triaged alert are integrated into the system: (i) an amber alert for symp-
toms of mild or moderate severity, which require a response within 4 h (or similarly
appropriate time period) of the alert and (ii) a red alert for severe symptoms, which
require a response within 30 min (or similarly appropriate time period) of receipt of
the alert.

An overview of the ASyMS infrastructure is provided in Figure 1.

With all versions of the ASyMS system, the main means of communication with the
patient is via a mobile device. The study server hosts the risk-alerting algorithms, and via a
web interface, provides a clinical portal for nurses to log into and track any alerts being trig-
gered, as well as view patient-specific information (for example, questionnaire responses, can-
cer type and stage, co-morbidity information) to help them make an informed decision about
how to deal with an alert.

Kearney and colleagues have conducted a significant body of work in relation to ASyMS
over recent years (Gibson et al., 2010; Kearney et al., 2006; Kearney et al., 2009; Maguire
et al., 2008a; Maguire et al., 2008b; Maguire et al., 2005; McCall et al., 2008; McCann
et al., 2009). The evolution of the system is evident both in terms of patient populations
using the system and the complexities associated with the study design in which the
feasibility, acceptability and impact on patient outcomes have been explored. The feasibility and acceptability of ASyMS has been demonstrated consistently from patient and professional perspectives (Maguire et al., 2008a; McCann et al., 2009). Developments across the lifespan of the work are further testament to this. The initial technological conception required patients to use a modem to send their symptom information to the clinical site via a handheld computer (Kearney et al., 2006). Subsequent work adapted the symptom questionnaire to specific patient populations [for example, patients with palliative care needs (McCall et al., 2008) and teenagers and young adults receiving chemotherapy (Gibson et al., 2010)]. Furthermore, ASyMS has demonstrated its potential to significantly impact on patient outcomes in a small-scale randomized controlled trial (RCT) study, in which decreased severity of fatigue and improved reporting of hand-foot syndrome was observed in the intervention group (Kearney et al., 2009).

5. Third generation ASyMS: The ASyMS-III study
As previously discussed, empirical evidence surrounding ASyMS is indicative of the potential for a telehealth system such as this to support people with cancer receiving chemotherapy. By allowing health professionals to respond in ‘real time’ to patients’ symptoms, ASyMS facilitates timely interventions and treatments. However, the evolution of this system is such that wider-scale implementation must now be demonstrated. As such, the ASyMS-III study has been designed to allow the impact of the system to be evaluated in a large-scale patient population.

5.1. Study design
The overarching aim of the ASyMS-III study is to evaluate, through the use of a pragmatic study design, the impact of ASyMS on the care delivered to people with breast and colorectal
cancer receiving adjuvant chemotherapy. The ASyMS-III study is a multi-site, complex intervention study, conducted over three phases, in which 312 patients are being recruited. Traditionally, evaluation of health-intervention systems has been conducted through use of a Randomised Controlled Trial (RCT) (Cummings & Turner, 2010). However, the quantitative techniques used to evaluate the impact of interventions in RCTs can restrict the amount of data collected (Bluhm, 2005; Grossman & Mackenzie, 2005) and are not always useful in evaluating complex interventions. The utility and validity of other approaches, such as the before-and-after study we have adopted, is now strongly recognized (Borgerson 2005).

As in our previous ASyMS studies, alerts are triaged to appropriate health professionals. In the ASyMS-III study, alerts that are deemed ‘amber’ are triaged to NHS 24. Alerts that are deemed ‘red’ are triaged to acute care. This system is depicted in Figure 2.

The primary hypothesis of the study is that patients using ASyMS have a lower number of days’ delay in their planned chemotherapy treatment regime, compared to patients receiving standard care alone. In order to demonstrate such an outcome, the study is exploring the impact of ASyMS on planned delivery of chemotherapy treatment, by determining the current state of chemotherapy delivery (including regime, dose and timing) in the clinical sites prior to and during the use of ASyMS.

In addition to the primary hypothesis, a number of secondary endpoints and outcomes are being explored in the study. These consist of patient-reported outcomes, such as symptom burden and self-care efficacy, processes of care delivery within acute cancer services and NHS 24, including health system costs and the impact of ASyMS on the nursing workforce. Each phase of the study has distinct aims and objectives, but all have been designed to facilitate systematic and rigorous evaluation of ASyMS, to inform its implementation into routine clinical practice.

![Figure 2. ASyMS III infrastructure.](image-url)
5.1.1. Phase I
In this first phase, current care prior to the introduction of ASyMS is analysed. A total of 150 patients are being recruited (n = 75 breast cancer, n = 75 colorectal cancer) to determine current models of care and outcomes of interest before the introduction of the ASyMS system into clinical practice in Phases II and III. This ‘before’ stage is being conducted over a period of 10 months, during which time the following objectives are being addressed:

- Determining current primary outcome and patient-reported outcome measures by conducting a review of patients’ case notes.
- Determining secondary endpoints using patient symptom diaries, and the following outcome questionnaires: Functional Assessment of Cancer Therapy (FACT-L): Fact-B (Breast Cancer) and the FACT-C (Colorectal Cancer) (Cella et al., 1993; Weitzner et al., 1995), Self Efficacy Scale (Lev & Owen, 1996), the 20-item State-Trait Anxiety Inventory (Speilberger, 1983), the 30-item Rotterdam Symptom Checklist (de Haes et al., 1996), and EQ5D (Rabin & de Charro, 2001). These questionnaires assess an individual’s quality of life, self-care ability, anxiety, symptom burden and health utility.
- Determining current systems of care using process of care mapping.
- Refinement of the ASyMS chemotherapy intervention for use in phases II and III of the study.
- Determining current health care costs related to the delivery of adjuvant chemotherapy to people with breast or colorectal cancer.
- Determining current workforce issues through use of established theoretical model-based questionnaires (Karasek et al., 1998; Siegrist, 1996).

5.1.2. Phase II
Phase II of the study will be conducted over a period of two months. The objective of Phase II is to pilot test the ASyMS intervention in 12 patients (six patients with breast cancer/six patients with colorectal cancer) in each of the clinical sites over one cycle of chemotherapy to:

- Assess the feasibility of the full-scale study.
- Assess whether the research protocol is realistic and workable.
- Establish whether the sampling frame and technique are effective.
- Assess the likely success of proposed recruitment approaches.
- Identify logistical problems which might occur using proposed methods.
- Assess the proposed data analysis techniques to uncover potential problems.
- Further test the technological integration of ASyMS within NHS 24 and participating sites.

5.1.3. Phase III
The objectives of Phase III of this study (the ‘After’ phase) are to evaluate the impact of the ASyMS intervention on the primary outcome measure, processes of care, health care costs, Patient Reported Outcome Measures, chemotherapy delivery (regime, dose, timing), and impact on the cancer nursing workforce. The methods adopted in Phase I to evaluate such measures will be employed. A total of 150 patients (n = 75 breast cancer, n = 75 colorectal cancer) will be recruited to Phase III of the study and will use the ASyMS system throughout their proposed chemotherapy treatment.
5.1.4. Data analysis

The primary analysis will consist of a comparison of the number of days’ delay in an individual’s planned chemotherapy treatment regime in those using ASyMS compared to patients receiving standard care alone. If the number of days of delay is approximately normally distributed this will consist of a t-test for the difference in means. If not normally distributed, a transformation will be assessed or non-parametric methods such as Mann-Whitney applied.

As there may be a number of confounding factors, multiple regression on the number of days’ delay as outcome will be utilised with before and after as a dichotomised factor in the model. Confounding factors are likely to be: stage at start of treatment, type of chemotherapy regime, tumour type (colorectal, breast), age, gender, deprivation, co-morbidity. Tests for interactions between factors and before/after will be carried out. The Akaike’s Information Criterion will be used to select models. These analyses will be repeated for the secondary patient-reported outcomes.

In addition to the before-and-after comparison, it will be possible to assess trends over time as measurements are made every 3 weeks, allowing an interrupted time series analysis to be carried out. In this analysis, changes in slope or intercept can be tested following the introduction of ASyMS, and hence can allow for secular trends prior to the intervention.

5.2. Study progress to date

Phase I of the study, where we are evaluating care prior to ASyMS use, is currently underway at eight NHS sites across Scotland, England and Northern Ireland. As part of this phase the following processes are being conducted:

5.2.1. Clinical and patient advisory groups

One key aspect of our research focuses on patient and clinician involvement. We believe regular interaction and discussion with patients and clinicians is paramount in ensuring that the tool developed is fit for its purpose, and meets current needs of patients and health professionals alike. At each site, patient and health professional advisory groups have been established and to date have advised on the content of the patient questionnaire, the suitability of the ASyMS alerting algorithm, self-care library content provided to patients, prototype interface design on the patient hand-held device and web system.

5.2.2. Mapping current care

Workshops have been conducted at each site to establish the current model of care in terms of a patient’s chemotherapy pathway and also the symptom management process. Workshop participants have included a cohort (approximately 7–15 participants) of health professionals involved with chemotherapy delivery.

5.2.3. Data collection and analysis

Patients participating in the study have been completing patient packs (consisting of questionnaires and patient diaries) providing an insight into their chemotherapy experience. Case note reviews of patients have been analysed and pertinent data extracted. An interim analysis of the data collected will be conducted at the end of Phase I.
5.2.4. Development of the ASyMS-III Real-Time Symptom Management Tool

Significant work has been conducted in the development of the ASyMS-III version of ASyMS. During systems development, we are engaging extensively with our clinical and patient advisory groups across participating sites. Through this process, we are attempting to capture and act upon feedback received, such that we anticipate when the system is given to patients and clinicians in Phases II and III, there will be few issues with regard to its acceptance and overall usability. However, the primary aim of Phase II of the project is to pilot the tool with a subset of patients, prior to issuing it to the full set in Phase III. Thus, if any issues do arise, these can be dealt with in a timely manner, without impacting Phase III of the project and the study design.

6. Future direction of ASyMS research

6.1. Use of ASyMS in different clinical settings

As previously highlighted, ASyMS has been applied to a number of varied patient populations. We are currently running a Phase I trial to identify the potential use of ASyMS with individuals with long-term conditions. We hope to publish results from this trial in December 2012.

6.2. Use of risk modelling to personalise toxicity predictions

ASyMS acts as a reactive system, triggering alerts to appropriate clinical staff when a patient experiences a symptom. Preliminary work has been conducted in the area of toxicity prediction, where the side effects a patient is likely to experience are predicted (along with a measure of certainty) prior to the side effect occurring (Cowie et al., 2006; Maguire et al., 2008a). We would like to further this work and explore the clinical value of this information, investigating how it might be incorporated into clinical care.

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