Randomised controlled trial to evaluate electronic Symptom Management using the Advanced Symptom Management System (ASyMS) Remote Technology for patients with cancers

Executive Summary:
Cancer incidence world-wide is set to increase by at least 65% over the next 20 years. The eSMART study is a pioneering research project focused on evaluating the impact of a remote symptom monitoring system (called the Advanced Symptom Management System – ASyMS) on chemotherapy related symptoms in patients with breast cancer, colorectal cancer and lymphoma across 5 countries in Europe (Austria, Greece, Ireland, Norway, United Kingdom). The eSMART study positively impacted on services and patient outcomes in these 5 countries by providing patients and professionals with a virtual method of support in the assessment and management of symptoms during chemotherapy in the home care setting.

During the study, participants were randomly allocated to receive either the remote monitoring system or to receive care as usual in their hospital. The eSMART study successfully recruited a total of 840 participants receiving chemotherapy treatment across the partner countries.

Patients allocated to the remote monitoring system (ASyMS) were provided with a mobile phone to monitor and record their daily chemotherapy symptoms and were also provided with a thermometer to take their temperature. Once this information was entered on the mobile phone, a set of rules within the system reviewed the symptom reports - if any reported were of concern, the system alerted the patient's health professionals at their hospital. On receipt of alerts, health professionals viewed a secure web page with patient's symptom and clinical information and where appropriate contacted patients via phone to offer further advice and support. When contacting patients, professionals used evidence-based guidelines embedded in the remote monitoring system to assist the management of symptoms. Patients also received self-care advice on the mobile phone advising them on how to manage the symptoms themselves. Participants used the remote monitoring system for a maximum of 6 cycles of chemotherapy.

To assess the impact of the remote monitoring system, all patients recruited to the study, irrespective of whether they were using ASyMS or not, completed a number of questionnaires asking them about symptoms, quality of life, supportive care needs, anxiety, work limitations and health service use. During treatment participants completed these questionnaires at the start of the study and at each cycle of chemotherapy treatment. They were also asked to complete the same questionnaires once they had stopped using ASyMS at 3-monthly intervals for up to 1 year.
The results of the eSMART study demonstrate that patients using ASyMS during chemotherapy treatment have better outcomes than patients in the treatment as usual group, and some of these benefits were still evident for a number of months after they stopped using ASyMS. The study also assessed the economic benefits of the remote monitoring system across the 5 countries providing useful information on the cost of the system compared to treatment as usual in the countries. Experiences of health professionals and patients using the remote monitoring system were also explored using interviews. Positive experiences of using the system and its impact on clinical care were reported.

An additional part of eSMART was to explore the use of existing data and that collected as part of eSMART to develop models to generate predictions of what chemotherapy-related symptoms an individual or a group of patients are likely to experience during their treatment. During the study the use of various predictive risk models were explored and revealed new insights into symptom experiences of people with cancer. These new insights can be used to optimise symptom assessment and management in the future. All results of the eSMART study are currently being prepared for publication in peer-reviewed journals and will be published soon.

Project Context and Objectives:
Over 3 million people are diagnosed with cancer each year in Europe and cancer incidence world-wide is set to increase by at least 65% over the next 20 years. Cancer is recognised as one of the most debilitating of chronic illnesses, not only because of its widespread impact on every aspect of patients’ and families’ lives but because of its repercussions on global economy associated with disability and premature death. Chemotherapy is a core treatment for cancer, however, its use can often lead to distressing and potentially life-threatening symptoms, which are associated with impaired quality of life (QoL), infections, increased mortality and poor treatment adherence. Such symptoms occur during treatment but can also persist into survivorship resulting in long-term burden for individuals and significant costs for the healthcare system. Traditional methods of symptom assessment in clinical care often rely on patients having to recall what symptoms they experienced since their last cycle of chemotherapy – which can fail to identify patients’ symptoms in a timely manner as they are not being reported as and when they occur. Poor symptom assessment and management results in impairments in quality of life and physical and psycho-social well-being, increased supportive care needs and increased time spent in hospital, which can negatively affect survivorship.

High symptom burden not only affects patients but also their families and carers. Carers of people with cancer often experience a host of adverse effects, including deficits in physical functioning and psychological well-being that can lead to absence from work, social isolation, and poor QoL.

eSMART used existing technology, the Advanced Symptom management System (ASyMS), to remotely monitor and manage symptoms experienced by people with cancer using mobile phones in the home setting. Once a day and at any time they felt unwell, patients completed a questionnaire on their mobile phone asking them about symptoms that they were experiencing. If any of the symptoms reported were of concern, health professionals in the patient’s hospital were immediately alerted. On receipt of an alert, health professionals logged onto a secure web page to view the patient’s symptom reports and contacted them for further management where appropriate. When calling patients to manage symptoms, health professionals used information on the ASyMS system to inform the management of symptoms. The ASyMS system also provided patients simple advice on how they could manage symptoms themselves. When and if required, ASyMS facilitated rapid entry into hospital for those patients experiencing more complex or life-threatening toxicities, providing quick access to specialist care and the initiation of appropriate and timely interventions. The model of care proposed through eSMART was therefore anticipatory and preventative and not reactive – as the system aimed to pick up and report troublesome symptoms early as and when they occur.

The main objectives of eSMART were to evaluate the short-term and long-term impact of ASyMS on symptom burden in people with breast, colorectal or haematological cancers receiving chemotherapy. Secondary objectives were to evaluate the impact of ASyMS on quality of life, supportive care needs, anxiety, self-efficacy, and work limitations. Another important objective was to evaluate the cost-effectiveness and changes in clinical practices as a result of the implementation of ASyMS in different European healthcare settings. An additional component of eSMART, not related to the main trial, was the development of risk models to predict the likelihood of individuals and groups of patients with cancer to experience specific symptoms related to their chemotherapy treatment. To this end, the project was divided into 6 work packages to achieve the aims and objectives detailed above. The specific work package (WP) context and objectives within the eSMART project are summarised below.

WP1: Integration of ASyMS within different Healthcare Systems across Europe
The aim of WP 1 was to prepare and adapt the ASyMS system for use across the 5 European countries and prepare the clinical sites for the integration and use of ASyMS during the main trial. To achieve this, 5 main activities were undertaken including a scoping review of the literature, a review of symptom management guidelines, translation of ASyMS components, pilot testing, and coordination of ethical and governance approvals.

The scoping review of the literature and of the guidelines relating to the assessment and management of chemotherapy related
symptoms across Europe ensured that the symptom questionnaires, rules to generate alerts, instructions for the management of symptoms and self-care included in the ASyMS system was evidence based and applicable in clinical practice in the 5 participating countries. Following this activity ASyMS was translated into the respective languages (Greek, Austrian German, Norwegian). The system was tested in each clinical site and each country with 2 patients per cancer type (breast cancer, colorectal cancer, lymphoma) to ensure readiness of the use of ASyMS during the main trial. This WP also coordinated the ethical and governance approvals for eSMART partners in all participating countries.

WP2: Demonstration of the Effects of ASyMS on Patient Outcomes during Chemotherapy Treatment
The aim of WP 2 was to conduct a multi-centre clinical trial to evaluate the effectiveness of ASyMS on pre-specified patient outcomes such as symptom burden, quality of life, supportive care needs, anxiety, self-efficacy, and work limitations during chemotherapy treatment. Patients with a diagnosis of breast, colorectal, or haematological cancer who met the overall inclusion criteria were invited to take part in the study. Participants were randomly allocated to receive either the ASyMS intervention (remote monitoring of symptoms) or care as usual. Participants allocated to ASyMS used the system up to and including 6 cycles of chemotherapy treatment. Other participants received care as usual. Outcome measures were assessed in both groups at the start of treatment and at each cycle of chemotherapy.

WP3: Demonstration of the Sustained Effects of ASyMS in the Year Following Completion of Chemotherapy
The aim of WP 3 was to evaluate the long-term effect of ASyMS on key patient outcomes for up to 12 months following the use of the ASyMS during active chemotherapy treatment. Participants from both study groups (with or without ASyMS) who continued in the follow-up period of the study were asked to complete the same questionnaires as used during the main study to measure symptom burden, quality of life, supportive care needs, anxiety, self-efficacy and work limitations at 3-monthly intervals up to 1 year.

WP4: Changes in clinical practice following the introduction of ASyMS
The aims of WP 4 were to assess the changes in clinical practice as a result of the introduction of ASyMS and to evaluate the cost-effectiveness of using ASyMS compared to usual care. Changes in clinical practice as a result of ASyMS were assessed with qualitative methods involving patients and clinicians. Several data sources were used for the cost-effectiveness calculations. The cost elements were valued using country specific information.

WP5: Predictive Risk Model to Deliver Personalised Care
This additional component of eSMART was not part of the main trial but aimed to look at ways to advance the understanding of the symptom experience by developing models using data that could predict what symptoms an individual or groups of patients were likely to experience at the start of and during chemotherapy treatment. This WP used data from previous supportive care studies carried out by the members of the collaborative and from the eSMART study and used an array of different types of analyses including mathematical modelling and artificial intelligence to develop the models. This WP also explored the perceptions of patients and professionals of the value of this type of information on daily life and symptom management in clinical practice.

WP6: Dissemination and Exploitation
The aims of WP 6 were to clearly communicate the projects’ progress and final results through presentations and publications so that critical information could be shared with internal and external stakeholders as well as with relevant institutions, organisations and the cancer care community. An exploitation plan was produced which outlined the implemented strategies and actions to disseminate and exploit the results generated by the eSMART study leading to ASyMS being a commercially viable solution in the future.

Project Results:
WP1: Integration of ASyMS within different Healthcare Systems across Europe
This work package had 5 main activities including a scoping review of the literature and guidelines relating to the assessment and management of chemotherapy related toxicity across Europe to ensure that the symptom questionnaires, rules to generate alerts, instructions for the management of symptoms and self-care was evidence based and applicable in clinical practice in the 5 participating countries. It also included translation of the ASyMS system in to the respective languages (Greek, Austrian German, Norwegian) and testing of the system in each clinical site with 2 patients per cancer type (breast cancer, colorectal cancer, lymphoma) in each country to ensure readiness of the use of the ASyMS system during the main trial. This WP also coordinated the ethical and governance approvals for eSMART partners in all participating countries.

The scoping review identified literature and clinical guidelines relevant to the management of symptoms and / or self-care of breast cancer, colorectal cancer and haematological cancers. Local symptom management protocols were also reviewed but only 6 of the 14 participating sites were available. This low availability was due to the fact that guidelines were not available in English, or no
institution-specific guidelines existed. From this review relevant clinical practice guidelines and evidence-based resources were identified for chemotherapy related symptoms including fatigue, chemotherapy induced nausea and vomiting, oral mucositis, diarrhoea, constipation, febrile neutropenia/neutropenic sepsis/infection, hand-foot syndrome, and pain. This information was built into the system to ensure that it was evidence-based and aligned with best practice across Europe. Based on this evidence, adaptations were then made to the content of ASyMS including the daily symptom questionnaire, the criteria for the generation of alerts to health professionals, clinical guidance for health professionals to manage symptoms and the evidence-based self-care advice given to patients and professionals. Consensus from all participating sites for the content of the ASyMS system was gained via clinical and patient advisory groups in each country. A total of 18 healthcare professionals and 24 patients across Europe participated in these groups. Their expert views were considered to make the final decision for the content of ASyMS to be used in the subsequent trial.

Preparation for ASyMS to be used in a European context also included translation of the system and supporting trial documentation into the respective languages. A number of questionnaires completed by patients also had to be translated. Clinical partners assisted in the translations to make sure they were appropriate and context specific. Based on the already developed infrastructure of the ASyMS technology, Docobo, the software development company, undertook a software update incorporating all the relevant information gleaned from previous processes (translations, scoping review, and clinician review). Docobo also designed manuals in all languages, provided technical support, and trained clinicians and partners on the use of the system.

Following the software update, health professionals at each participating site were trained on the trial processes and how to use the system. Prior to initiation of the full RCT, each clinical site carried out a pilot study. As part of this pilot study, several technical aspects of the ASyMS system were tested. First, the nurse handsets (mobile phones for nurses to view patient alerts) were tested for connectivity within the clinical site to ensure that alerts could be received and patient reports viewed on the secure and dedicated health professional web based system. The connectivity analysis found that all sites apart from one site demonstrated a reliable communications environment. Issues at the one site were fixed and connectivity was improved. After connectivity at clinical sites was satisfied, a small sample of patients with breast cancer, colorectal cancer or lymphoma were recruited for the pilot study at each participating site. During this pilot study randomisation procedures were tested and participants were allocated to receive either the remote monitoring symptom system of care or care as usual according to their hospital. Patients allocated to remote monitoring of their symptoms used ASyMS for over one cycle of chemotherapy. During the feasibility study some issues arose which were categorised as clinical or technical issues. These centred around concerns regarding red alert triggers, lack of clarity around documentation, limited opportunity to enter additional information in the daily electronic symptom questionnaire, and issue of over-reporting symptoms. Modifications were made to ASyMS and associated documentation after consideration of the clinician feedback. These included changes to the clinical algorithm for some symptoms, modification to the alerting process, and the addition of more detailed information about the questionnaires in the Patient Information Sheet. A small number of technical issues were identified. These were technology not operating as intended, design flaws such as synchronising issues, and training and documentation where users did not fully understand the processes. All issues were addressed and resolved. After each site was formally evaluated and found to be in a position to move to WP2, they were issued with a letter from the Chief Investigator to move to WP2. More details about the feasibility study, the study protocol, and a scoping review can be found in scientific publications which resulted from WP1:

- BMJ Open 7. doi:10.1136/bmjopen-2016-015016
- JMI Cancer 5. doi:10.2196/10813

The eSMART study was conducted in accordance with the study protocol, the UK Data Protection Act, 1998, and the guiding principles of the Declaration of Helsinki. Due to the multi-national setting of the eSMART study it was essential to determine standardisation and transparency of information across all European sites. First, ethics permissions were sought from the United Kingdom ethical governance (National Health Service Research Ethics Committees [NREC]). After receipt of favourable ethical opinion all from the UK governance and then all non-UK partners were required to submit their application to their respective Research Ethics Committees (REC) and academic institutions (if appropriate).

WP2: Demonstration of the Effects of ASyMS on Patient Outcomes during Chemotherapy Treatment

WP2 was conducted during 2016-2018. The trial enrolled a total of 840 participants undergoing chemotherapy in five countries. Seven in the intervention group and four in the usual care group were either found to be ineligible after randomisation or immediately withdrew consent leaving 415 and 414 analysable respectively. Withdrawal was lower than expected during the trial with 34/415 (8.2%) in the group receiving the mobile phone and 38/414 (9.2%) in the usual care group. The average age was 52 years with 81.8% female. Breast cancer was the most common cancer (71.4%), followed by colorectal cancer (18.3%) and haematological cancers (10.2%). Cancer stage was II or lower in 53.4%, 37.4% stage III, 2.5% stage IV with 6.8% missing. Patients were enrolled in five countries; UK (31.7%), Greece (31.2%), Austria (16.9%), Ireland (16.3%) and Norway (3.9%). Co-morbidities were absent in 50% and only 2% had five or
more co-morbidities. Adverse events were generally balanced across the two study groups. There were 3 deaths in each group in the study. Neutropenic events (low white count, infection) were not surprisingly higher in the intervention group. There were similar numbers of planned and unplanned hospitalisations in both groups.

Results of WP 2 indicate that ASyMS showed positive effects in the majority of outcome measures in favour of the group that used the ASyMS system. Such results demonstrate the positive impact of the ASyMS system during active chemotherapy treatment on patient outcomes. As the results of WP 2 have not been published yet, the detailed quantitative findings are kept temporarily confidential until publication.

WP 3 Demonstration of the Sustained Effects of ASyMS in the Year Following Completion of Chemotherapy

WP 3 aimed to evaluate the long-term effect of ASyMS on key patient outcomes for up to 12 months following the use of ASyMS during active chemotherapy treatment. A total of 757 participants entered the follow-up phase, which represents 90% (757/840) of those who took part in the main trial. Because of this high entry into the follow-up the balance of patient characteristics through allocation to each study group (remote monitoring system or usual care) was generally maintained into the follow-up.

Results indicate that ASyMS demonstrated positive effects on some outcomes for a number of months following the use of the system during active chemotherapy treatment. As the results of WP 3 have not been published yet, the detailed quantitative findings are kept temporarily confidential until publication.

WP 4: Changes in clinical practice following the introduction of ASyMS

To understand the impact of the ASyMS technology and model of care on clinical practice, a range of additional data were gathered to complement the quantitative trial data collected in WP2, WP3 and the cost-effectiveness component of WP4. This data included some assessment of existing clinical guidelines and their use at clinical sites and a baseline survey with clinical staff prior to the introduction of the intervention to gain an overarching perspective on the use of technology within clinical care at that time. Then, to better understand the realities of using ASyMS and its impact on clinical practice, a series of post-participation interviews were conducted with patients and clinicians from each of the partner countries.

Review of symptom management protocols: Of the twelve clinical sites engaged in the study, just six were able to provide specific details on the use of symptom management protocols at their site. Sites which reported use of symptom management protocols drew on a combination of international, national and local policy driven practices, but there was considerable variability in the application of these across the sites. Therefore, the challenge for the eSMART Consortium in the initial phases of the programme of work was to reach consensus across the clinical sites in all countries in relation to the symptom profile contained within the DCTAQ and the alerting algorithms embedded within ASyMS. For some sites this would be the first time they worked to detailed and structured protocols and for all sites it was the first time they worked to protocols consistent across a range of European countries.

Assessments of changes in clinical practice: A study-specific questionnaire was distributed to clinicians across the clinical sites at baseline – before they started to use ASyMS – to capture their perceptions on the role of technology in healthcare, their experiences of using technology in healthcare settings and their expectations for ways in which ASyMS would impact on clinical practice. To understand experiences of using ASyMS at follow up – after exposure to ASyMS - we conducted a range of 1-1 interviews with patients and clinicians (47 qualitative interviews in total).

Analysis of the qualitative data gathered revealed a central orienting theme of ‘ASyMS as a facilitator for change’. On the whole, it was evident that ASyMS was perceived positively by patients and clinicians across the eSMART partner countries. We know from the collective data from the eSMART programme of work that ASyMS has demonstrated real, positive and significant improvements to the lives of people with cancer during chemotherapy treatment and can positively disrupt clinical practice to provide patients with improved cancer care experiences.

WP 4: Economic Evaluation

For the patient reported questionnaires used in this component of the study baseline data were available on 780 patients. During the treatment phase the maximum number of related patient questionnaires completed at a given time-point was 786. Data were available on 534 patients over follow-up. The mean cost of the intervention was €214 per person over the treatment period across all countries. The mean number of days of treatment was 113 per person.

Service use and costs: Inpatient use: During the three-month period prior to baseline assessment, similar proportions of each group used inpatient care. However, there were clear differences between countries with much higher levels of inpatient use in some countries compared to others. For those who were admitted to hospital, the mean number of days was generally similar between groups. The costs of inpatient care were high compared to other services. During the follow-up the use of inpatient care was similar between groups in each country.

Outpatient use: At baseline the levels were similar across the majority of countries. For those with outpatient contacts, the average number of visits was similar for four out of the 5 countries taking part in the trial.

Tests and investigations: There were high rates of tests and investigations (including MRIs, CT scans, blood tests, x-rays) in each country and at each time point. Costs were far higher in the UK than other countries, particularly Greece.

Emergency department: Visits to emergency departments were made by relatively few participants at baseline, but with somewhat
higher use in the UK.

Other services: Relatively few participants reported having received other health and social care services at baseline. The highest rates of use were for the UK, but this still only represented around one-third of those participants. During active treatment there was more use of other services in each country but without substantial differences between groups. During the follow-up period, use was maintained at similar levels to the previous period, but with more use in the ASyMS group.

Total costs: At baseline the total mean costs were relatively similar between the two groups and with no significant differences. The ‘quality adjusted life year’ was higher in the ASyMS across countries apart from one country. During the intervention phase, mean costs were higher for ASyMS in four out of the five countries. However, none of the differences were statistically significant.

As the results of the economic evaluation have not been published yet, the detailed findings are kept temporarily confidential until publication.

WP5: Predictive Risk Model to Deliver Personalised Care

Several methods were applied to achieve the objectives of WP5. The statistical approaches included standard mathematical and artificial intelligence approaches. Interview and focus groups with patients and clinicians were conducted to explore the clinical utility of predictive risk models (PRMs).

A total of 4 different analyses were carried out to provide additional and new insights into the symptom experience of patients with cancer. These analyses provided information on what approaches were most appropriate to develop predictive risk models for cancer related symptoms, identified patient characteristics associated with a high symptom burden and identified associations between groups of symptoms.

The clinical utility of predictive risk models developed during this WP was explored with qualitative interviews. Across the 5 countries, 26 clinicians and 28 patients with a diagnosis of breast, colorectal or haematological cancer took part. A mixture of focus groups and interviews was carried out. Overall, patients saw benefits in the ability of predicting the likelihood of experiencing specific symptoms. Benefits were around education, information, and feeling more prepared and in control. The additional knowledge could also benefit their family members by letting them know what symptoms individuals could expect. However, some patients expressed some negative perceptions viewing insight into symptoms that they were most likely to experience as running the risk creating a negative mindset. Clinicians also expressed great benefit of having predictive risk models available to inform the care of their patients particularly in the delivery of personalised symptom management. Like patients they had some negative perceptions such as trusting the evidence base underpinning the models and their ability to deal with the complexities of the cancer patient experience and support the delivery of holistic care.

WP6: Dissemination and Exploitation

Several dissemination channels were used to reach different stakeholder groups. Different channels were used based on the audience and the information that was disseminated. A project website was created which was used to raise awareness of and interest in the study and its results. The website contains a summary of the study, a description of objectives and expected results, participants’ descriptions, contact details and links to their and other websites (see below for website link). Social media channels were used as a cost-effective way of sharing immediate updates from the project to lay and expert audiences, targeting both existing and new contacts. Several YouTube videos were released to target wider audiences including citizens and the public (https://www.youtube.com/watch?v=ma8l0ZCUcS1 https://www.youtube.com/watch?v=wD0AAHrH_Gs).

Other communication strategies that were used include press releases, and magazine articles. A project newsletter was published on a regular basis to share progress, news, events and outcomes of the study. In total 20 newsletters were published and each clinical site took responsibility to publish at least one newsletter. In total, 7 peer-reviewed journal articles were published with work from the eSMART consortium. Publications appeared in the following journals:

- European Journal of Cancer Care (Impact factor:2.421)
- European Journal of Oncology Nursing (Impact factor:1.697)
- BMJ Open (Impact factor:2.376)
- Journal of Pain and Symptom Management (Impact factor:3.249)
- Plos One (Impact factor:2.196)
- Scientific Reports - Nature (Impact factor:4.129)
- JMIR Cancer (Impact factor: 4.945)

A final conference was held on the 5th of July 2019 in Brussels, Belgium to share preliminary results of the eSMART study. The conference was attended by over 70 participants representing a mix of visitors from politics, academia, industry, and healthcare.

Description of the potential impact (including the socio-economic impact and the wider societal implications of the project so far) and
the main dissemination activities and the exploitation of results

Potential Impact:
Given the substantial increase in the number of people with cancer who will receive chemotherapy and the transition of cancer services from traditional in-patient care towards care delivered within local settings, the eSMART study has provided a more effective solution to deliver supportive care to ensure optimal patient outcomes. It is anticipated the findings from the eSMART study will transform how patients receiving chemotherapy are monitored in the future and will have a significant impact on the lives of people with cancer receiving chemotherapy.

Cancer costs the European countries 124 billion Euros every year, according to the estimate of the full economic burden of the disease in the European Union. The economic toll of cancer is also high due to economic losses from premature death, disability, and chemotherapy-related toxicities.

Utilising real-time remote patient monitoring will result in changes in clinical practice that improve the delivery of care, reduce health care costs and demonstrate the value of an anticipatory and personalised model of cancer care. This will result in a shift in clinical practice and facilitate the provision of clear lines of real-time communication between patients and their health care providers to enable care to be effectively triaged and clinicians to employ a preventative and anticipatory model of care through identification of patients at greatest risk of adverse events of cancer treatment.

List of Websites:
The eSMART Study website is at https://www.strath.ac.uk/science/computerinformationsciences/esmart/.

Contact details are
eSMART, Computer & Information Sciences, Livingstone Tower, 26 Richmond Street, Glasgow, G1 1XH, UK

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