Real Time Remote Symptom Monitoring Reduces Patient Reported Symptom Burden During Adjuvant Chemotherapy Treatment: Results from eSMART, A European Multicentre Randomised Controlled Trial, using ASyMS remote monitoring technology for patients with cancer.

Journal:	*BMJ*
Manuscript ID	BMJ-2021-065142.R1
Article Type:	Research
Date Submitted by the Author:	22-May-2021
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Keywords:	Symptoms, Cancer, Chemotherapy, Web-based intervention

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Abstract

Objectives: To evaluate the effects of remote monitoring and management of adjuvant chemotherapy-related side-effects via the mobile phone based Advanced Symptom Management System (ASyMS) on patients' perceived symptom burden, health related quality of life, supportive care needs, state trait anxiety, self-efficacy, and work limitations.

Design: Multicentre, repeated measures parallel groups evaluator-masked stratified randomised controlled trial (RCT) conducted over a period of 36 months.

Setting: Twelve cancer centres across Austria, Greece, Norway, Republic of Ireland and United Kingdom.

Participants: 829 evaluable patients with non-metastatic breast cancer or colorectal cancer, or Hodgkin's Disease or non-Hodgkin's lymphoma receiving first-line adjuvant chemotherapy treatment or receiving chemotherapy treatment for the first time in the last five years.

Intervention: Patients were randomised to daily self-reporting of chemotherapy and temperature using ASyMS (intervention group) or standard care (control group) over 6 cycles of chemotherapy. In the intervention group, evidence-based clinical algorithms within ASyMS analysed patients' symptom self-reports and temperature values and when appropriate, generated alerts in 'real time' to clinicians prompting review and management through embedded evidence based clinical decision support system. Patients also received tailored, evidence-based self-care advice on the ASyMS device.

Primary outcome: Change in symptom burden scores from the Memorial Symptom Assessment Scale (MSAS) measured at baseline and up to six subsequent cycles using an adjusted mixed model analysis. Assessment of outcomes was blinded, and analysis undertaken on an intention to treat basis.

Secondary outcomes: Change in health related quality of life (FACT-G), supportive care need (SCNS-SF34), state trait anxiety (STAI-R), self-efficacy (CASE-Cancer) and work limitations (WLQ).

Results: For the intervention group, the primary outcome, symptom burden remained at pre-chemotherapy treatment levels, while the control group reported an immediate increase in MSAS total symptom burden from cycle 1 onwards: the adjusted mixed model gave a least squares mean difference of -0.15 (95% CI -0.19 to -0.12, $p < 0.0001$; effect size = 0.5) in favour of the intervention. Analysis of the MSAS sub-domains indicated significant reductions in favour of the intervention, for: the global distress index (-0.21, 95% CI -0.25 to -0.15, $p<0.0001$); psychological domain (-0.16, 95% CI -0.23 to -0.10, $p<0.0001$); and physical symptom domain (-0.21, 95% CI -0.26 to -0.17, $p<0.0001$). Relative to secondary outcomes, FACT-G scores were higher in the intervention group than the standard care group across all cycles (Mean difference=4.06, 95% CI 2.65 to 5.46, $p<0.0001$), while mean scores for STAI-R trait anxiety were lower in the intervention group (-1.15, 95% CI -1.86 to -0.44, $p=0.002$) and as well as STAI-R state anxiety (-1.05, 95% CI -1.95 to -0.16, $p = 0.020$) relative to standard care. CASE-Cancer scores were higher for intervention (0.81, 95% CI 0.19 to 1.43, $p=0.010$). Supportive care needs tended to be lower for all SCNS-SF34 domains for the intervention group in particular, sexuality needs (-1.56, 95% CI -3.11 to -0.01, $p = 0.048$), patient care and support needs (-1.74 95% CI -3.31 to -0.16, $p=0.03$), and physical and daily living needs (-2.8, 95% CI -5.0 to -0.6, $p = 0.013$). Other SCNS-SF34 and WLQ domains were not statistically significantly different. The safety of the ASyMS system was satisfactory with no device-related incidents reported. Adverse events were generally balanced across the two groups in terms of number of deaths and planned and unplanned hospital admissions. Neutropenic events were higher in the intervention group.

Conclusions: The significant reduction in symptom burden evidenced in this RCT supports the use of electronic systems such as ASyMS for remote symptom monitoring and management in routine cancer care. An effect size of 0.5 points to a sizable, positive clinical impact of ASyMS on patients' symptom experiences during chemotherapy. Remote monitoring systems will be vital for cancer services in the future, particularly with the shift to blended models of supportive care delivery in response to the COVID-19 pandemic and beyond.

Trial registration

Clinical Trials.gov NCT02356081.

Introduction

Over 14 million people worldwide are diagnosed with cancer annually; this figure is predicted to increase to more than 23 million by 2030 (Ferlay et al., 2015). Chemotherapy is a core anticancer treatment and recent advances have improved overall cancer survival rates (Ferlay et al., 2019). Despite guidance for patients and professionals on managing chemotherapy, symptoms during treatment continue to be poorly controlled in many patients (Devlin et al., 2017, Fox et al., 2017). This undertreatment results in poorer treatment adherence, impaired health-related quality of life (HRQoL) and increased health service utilisation and treatment-related mortality (Sheng et al., 2019, Tai et al., 2017, Coolbrandt et al., 2011). Toxicities experienced during chemotherapy treatment often persist into survivorship, have a negative impact on individuals and their families and generate significant costs for healthcare systems worldwide (Mittmann et al., 2018, Lagergren et al., 2019). While effective symptom monitoring and management is paramount, current assessment mechanisms rely on patients recognising that symptoms are severe enough to warrant reporting to clinicians. Uncertainty, delayed reporting, or inability to access 24-hour support services frequently lead to toxicities not being reported and managed within a safe time period, placing patient safety at risk (Curcio, 2016, Oakley et al., 2017). Solutions are needed that identify and manage chemotherapy toxicities in a timely manner to improve patient outcomes and reduce costs.

The advent of connected health (Loiselle and Ahmed, 2017, Lehoux et al., 2019) created a rapid proliferation of person-centered digital solutions to support patient management in community settings. This approach is particularly relevant to people receiving chemotherapy as it is often administered on an ambulatory basis. The use of real-time remote monitoring to assess toxicities overcomes many challenges to effective symptom management that often entail retrospective assessment, are subject to recall bias, and are argued to '*provide a weaker insight into actual symptom burden*' (Coolbrandt et al., 2011). These digital systems enable patient-reported data to be relayed to clinicians within minutes. This rapidity enables proactive symptom management with symptoms identified and managed early in their trajectory.

Digital remote monitoring systems have been developed and tested for chemotherapy treatments (Mooney et al., 2017, Absolom et al., 2021). Studies highlight benefits of these systems for quality of life (HRQoL), symptom alleviation, prevention of unscheduled hospital admissions, improved survival (Basch et al., 2016, Denis et al., 2019) and cost-effectiveness (Lizée et al., 2019). However, much of the evidence to date is derived from trials that included people with advanced disease, were of short duration, often from a single site/country and most lack health economic evaluation (Osborn et al., 2020, Moradian et al., 2018). Furthermore, limited focus is placed on generating evidence to inform scale up of these digital interventions across multiple settings and countries to enable the benefits to be realised within routine cancer care delivery worldwide (Lennon et al., 2017).

eSMART is a European trial that aimed to address limitations in research to date and provide definitive high-quality evidence of the large-scale benefits of remote monitoring in the assessment and management of adjuvant chemotherapy treatment. eSMART was underpinned by earlier work, in accordance with the Medical Research Council's framework for the design and evaluation of complex interventions (O'Cathain et al., 2019, Shahsavari et al., 2020) that demonstrated the feasibility and acceptability for patients and clinicians of remote monitoring of cancer treatment related symptoms using the mobile phone based Advanced Symptom

Management System (ASyMS) (Kearney et al., 2009, Maguire et al., 2014, Maguire et al., 2008, McCann et al., 2009).

The aim of eSMART was to evaluate, at scale, the effect of remote monitoring and management of adjuvant chemotherapy treatment on patient outcomes. The trial hypothesis was that ASyMS would lead to significant reductions in symptom burden, supportive care needs, anxiety, and work limitations and improvements in HRQoL and self-care self-efficacy during chemotherapy treatment in patients with breast cancer, colorectal cancer or Hodgkin's Disease (HD), or non-Hodgkin's lymphoma (NHL) receiving first line chemotherapy treatment over six cycles compared with standard care.

Methods

This European multicentre, parallel group randomised controlled trial (RCT) using 1:1 allocation recruited participants between 31st March 2016 and 14th December 2018. Data collection ceased on the 31st of March 2019. A detailed study protocol has been published (Maguire et al., 2017). No significant changes were made to the methods during the trial. The trial was registered on *ClinicalTrials.gov* (NCT02356081) and received NHS Ethics (ID: 14/SS/1062), NHS R&D approvals and local clinical site ethics approvals in each partner country prior to initiation. A Data Monitoring Committee was established to monitor the progress and safety of the trial and met on average 6 monthly during the RCT. The study is reported in accordance with the CONSORT statement for Randomised Controlled Trials.

Setting and patients

Patients were recruited from 12 cancer centres across Austria, Greece, Ireland, Norway, and UK. Clinical staff at each cancer centre and/or dedicated research staff assisted with recruitment. Patients who agreed to participate attended the cancer centre for an enrolment visit prior to their first chemotherapy treatment appointment. Written informed consent was obtained at the enrolment visit.

Eligible patients were: aged over 18; diagnosed with breast cancer or colorectal cancer or HD or NHL; scheduled to receive at least 3 cycles of 2-, 3- or 4-weekly first line adjuvant chemotherapy; physically and psychologically fit to participate and able to understand and communicate in the respective language of the country where recruited.

Patients were ineligible if they: had distant metastasis (breast or colorectal cancer) or B symptoms (HD/NHL); were receiving concurrent radiotherapy or weekly chemotherapy (as timeframes covered by the outcome measures were incompatible with weekly administration); had been diagnosed with cancer or received chemotherapy within the previous 5 years or were unable to provide informed consent.

As ASyMS aims to manage chemotherapy-related side-effects, the inclusion criteria were intentionally narrow to ensure only participants treated with curative intent would be recruited, rather than a heterogeneous sample that would also experience symptoms associated with advanced cancer.

Patients were initially recruited to participate in the RCT phase of the study for the full duration of their chemotherapy treatment. However, after 5 months of recruitment, this was amended to participation for up to a maximum of 6 consecutive cycles of chemotherapy to support recruitment and associated study timelines. This change was supported by previous ASyMS

pilot work (unpublished) which concurs with other literature (Brant et al., 2011) that chemotherapy-related symptoms are at their greatest during the first few cycles of treatment. This meant that participants utilised the intervention when they were likely to gain most benefit from it.

Outcome Measures

All participants completed patient-reported outcome measures (PROM) for both primary and secondary outcomes at baseline (T0) (enrolment visit prior to chemotherapy) and before each subsequent chemotherapy treatment for up to a maximum of six cycles. The baseline assessment preceded treatment allocation. PROM data were collected in the cancer centre, via a tablet computer or a secure weblink, prior to each chemotherapy treatment and coincided with visits for chemotherapy.

Additional data on adverse events, planned and unplanned admissions were collected by clinicians through the completion of a case note review prior to each chemotherapy cycle, reflecting events of the previous cycle. Specifically, a 'neutropenic sepsis event' was defined as the development of fever (oral temperature >38.5°C or two consecutive readings of >38.0°C for 2 hours) and other signs of generalised, whole-body infection in a patient with neutropenia (an absolute neutrophil count of less than 0.5×10^9/litre, or less than 1.0×10^9/litre and 'falling'). Hypothermia in the presence of neutropenia was also investigated as a sign of neutropenic sepsis (de Naurois et al., 2010). Device related incidents were monitored throughout the duration of the trial in accordance with the European Commission DG Enterprise and Industry guidelines on a medical devices vigilance system (http://www.meddev.info/_documents/2_12_1-rev_6-12-2009_en.pdf).

Primary Outcome Measure:

Memorial Symptom Assessment Scale (MSAS) (Portenoy et al., 1994): The MSAS measures 32 physical and psychological symptoms associated with cancer and its treatment including their frequency, severity, and distress/bother in the preceding week. Respondents were asked to indicate if they had experienced each symptom in the past week (i.e., symptom occurrence). If so, they rated its frequency, severity, and distress. A total MSAS score, representing symptom burden, was calculated by averaging all 32 items with potential range of 0-4. If >13% of items were missing the score was treated as missing (Portenoy et al., 1994). In addition, three subscale scores (i.e., Global Distress Index (MSAS GDI), physical (MSAS PHYS), psychological (MSAS PSYCH) were calculated and treated as secondary outcomes. The reliability and validity of MSAS are well established, and in this study the Cronbach's alphas for the Total MSAS, MSAS PHYS, MSAS PSYCH and MSAS GDI subscales and were 0.87, 0.82, 0.77 and 0.83, respectively.

Secondary Outcome Measures:

Full details of secondary outcomes measures are published in the eSMART study protocol (Maguire et al, 2017). Briefly they included:

- Functional Assessment of Cancer Therapy-General (FACT-G) (Cella et al., 1993). The 27-item FACT-G assesses overall health-related HRQoL in patients undergoing cancer therapy as well as four domains of well-being, i.e., physical, social/family, emotional, and functional well-being.

- Supportive Care Needs Survey Short-Form (SCNS-SF34) (Boyes et al., 2009). This 34-item instrument measures current supportive care needs in five domains: health

system and information, psychological needs, physical and daily living, patient care and support, and sexual-related.

- State-Trait Anxiety Inventory-Revised (STAI-R) (Spielberger et al., 1983) measures two types of anxiety (i.e. state (about an event) and trait (anxiety as a personal characteristic). Each scale comprises 20-items.
- Communication and Attitudinal Self-Efficacy scale for cancer (CASE-Cancer) (Wolf et al., 2005) assesses cancer patients' confidence and ability to engage in their care (i.e., self-efficacy). Twelve items contribute to three dimensions (i.e., maintaining a positive attitude, understanding, and participating in care, seeking and obtaining information).
- Work Limitations Questionnaire (WLQ) (Lerner et al., 2002) consists of 25 items that correspond to four domains (i.e., time management, physical demands, mental/interpersonal, output demands). The WLQ was only completed by those individuals who were working.

Additional secondary outcomes of the eSMART trial were to assess the effectiveness of ASyMS during the 12 months after completing the RCT, to evaluate the cost-effectiveness of the ASyMS intervention in managing chemotherapy-related symptoms and to assess changes in clinical practice due to using ASyMS. These secondary outcomes will be reported in separate publications.

Randomisation & blinding

Randomisation was performed remotely and independently by Surrey Clinical Trials Unit (a UK CRC registered CTU) using the Promasys system after patient consent and completion of baseline PROMs and prior to the first chemotherapy cycle. Randomisation was stratified by site and cancer type. Research staff accessed the Promasys system remotely, completed a web-based electronic case report form for the participant and the allocation was assigned automatically. Random allocations were programmed by statisticians at the CTU using proc plan in SAS®, and run by staff independent of the trial team to ensure allocation concealment. Due to the nature of the intervention, blinding of patients was not possible but patients were blinded to study hypotheses. However, blinding of evaluators was achieved as participants' allocation was concealed from the statistical analysis team.

The Intervention

ASyMS (see Figure 1) is a remote symptom monitoring system that provides real-time, 24-hour monitoring and management of chemotherapy-related side-effects. In brief, patients used ASyMS to complete a validated self-report questionnaire(Daily Chemotherapy Toxicity Self-Assessment Questionnaire (DCTAQ)) that evaluates 10 chemotherapy-related symptoms (i.e. feeling sick, being sick, diarrhoea, constipation, sore mouth and/or throat, paraesthesia, sore hands and/or feet, flu-like symptoms/infection, tiredness, pain) (Maguire et al., 2018). Participants could record six additional symptoms through the 'any other symptoms' functionality. They were asked to take and enter their temperature using a digital thermometer provided to them. Participants could also access tailored, evidence-based self-care advice about managing chemotherapy symptoms (adapted from Macmillan Cancer Support resources) on the ASyMS device at any time.As this study took place in several countries the intervention was translated into the native language of each site. This includes all aspects of the patient handset, the nurse handset, the website, the PROMs and the manuals. Patients completed the

DCTAQ daily and at any time they felt unwell for a maximum of 6 cycles of chemotherapy. This 'real-time' self-report was sent via a secure connection to the ASyMS server hosted by Docobo (https://www.docobo.co.uk/).

Following a review of local, national and European best practice guidelines for symptom assessment and management, an evidence-based clinical decision support system, incorporating a symptom alerting algorithm and symptom specific management protocols, was developed for ASyMS, and was subject to expert consensus by cancer clinicians and Principal Investigators from each clinical site prior to use (further detail is provided elsewhere Furlong et al., 2019) (see supplementary file 1).

Symptom data were automatically evaluated in ASyMS by applying the evidence-based algorithm which generated alerts, where necessary, to nominated clinicians in their respective cancer centres. The system triggered two types of alerts. Amber alerts were for persistent mild to moderate symptoms for which early intervention could prevent progression. Red alerts denoted chemotherapy emergencies such as signs and symptoms of neutropenic sepsis. When an alert was generated before an earlier alert was actioned (e.g., if the patient completed a 'subsequent DCTAQ because their symptoms had worsened) then the alerts were linked. The most up to date information about participants' symptom reports was displayed on the system and only the most recent linked alert was available for actioning.

Clinicians received alerts on a dedicated ASyMS clinician mobile phone. The required response times were 8 hours for amber alerts and 30 minutes for red alerts. On receipt of an alert, the clinician viewed patients' symptom reports on a secure web server, before making contact with the patient to initiate symptom management. During calls with patients, clinicians worked through an evidence-based clinical decision support system embedded within ASyMS to inform symptom management interventions.

Intervention group

Participants allocated to the intervention group used ASyMS for a maximum of six cycles. They were trained by researchers/clinicians at each site on its use prior to commencing chemotherapy treatment and given an instruction booklet to support use at home.

Standard care group

Patients allocated to standard care received care as usual at their cancer centre and were advised to contact their clinician(s) through standard mechanisms (usually telephone triage) if symptomatic. This group received clinical input in line with each local site's standard advice (verbal and written) on chemotherapy-related symptoms and self-care. As per local procedures, they were given information on how to contact their clinician(s) if they needed assistance with symptom management.

Sample Size

There are no known cut-off scores for the MSAS to indicate clinically important change. At the time of planning the eSMART trial, only limited literature was available, and it only focussed on the short version of MSAS (MSAS-SF) and on single patient groups followed over time. Chang et al. (2004) reported effect sizes (ES) of 0.20-0.66 for a change in total MSAS-SF scores from baseline to 1 week later, while Dapueto et al. (2014) reported an ES of 0.71 for a change in MSAS-SF GDI scores between the first cycle and third month of adjuvant chemotherapy. Given the absence of data on MSAS from intervention studies, a priori we considered a small-to-moderate ES of 0.25 to be the cut-point for a clinically significant

difference in total MSAS scores. Sample size estimation was then based on differences in total MSAS scores between intervention and control groups of 1.45-1.30=0.15 from a previous RCT (Ruland et al. 2013). For a difference in total MSAS scores of 0.15 (SD=0.6) and an ES of 0.25, with baseline and 4 repeated measures after enrolment, a sample of 776 participants (110 participants with Hodgkin's Disease or non-Hodgkin's lymphoma, 333 participants with breast cancer and 333 patients with colorectal cancer) were needed to provide 90% power for a 2-sided hypothesis test at the 5% significance level. To allow for 30% attrition, the total study sample size was increased to 1108. By February 2017, the attrition rate was lower than anticipated (10%), therefore the sample size was reduced to 862.

Data Analysis

An intention-to-treat analysis was performed. All analyses were undertaken by the trial statistician or a nominated delegate. Study outcomes are presented as means and standard deviations (SD) or percentages and denominators. Transformations were required when the distributions were non-normal and are presented as medians and minimums and maximums. Enrolment characteristics are presented for the evaluable intention-to-treat sample. The primary outcome of total MSAS score is continuous and was assessed in a repeated measures analysis using linear and non-linear mixed models. A mixed model repeated measures analysis that uses all available data, assuming data are missing at random (MAR), was used throughout the analyses. Many participants rated their symptoms as not present (i.e. 0) so the mixed model was implemented with a zero inflated gamma distribution and identity link to provide results on the original scale.

Analyses tested the between group difference in means for the primary outcome total symptom burden (total MSAS) during chemotherapy for a maximum of six cycles. The primary hypothesis (reduced symptom burden in the intervention group over a maximum of six chemotherapy cycles) was tested through the regression parameter for the intervention versus standard care group, adjusting for baseline MSAS. We also adjusted for pre-specified variables, namely: cancer type (breast cancer, colorectal cancer, HD, NHL), age (years), gender (male, female), number of co-morbidities (0, 1-4, 5+), and country (Austria, Greece, Republic of Ireland, Norway and the UK). Pre-specified subgroup analyses were assessed by fitting trial arm by subgroup interaction parameters. If this test was significant at the 5% level, results were estimated separately for the different subgroups.

SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA) and R 3.5 were used for all statistical analyses. A two-sided p value of <0.05 was be taken as significant for all analyses unless otherwise specified.

Patient and Public Involvement

The European Cancer Patient Coalition were partners in eSMART and advised prior to and throughout the duration of the study. They were involved in setting research priorities, defining research questions and outcome measures, and providing input into recruitment methods, data collection and dissemination. Results will be disseminated to this patient organisation but it is not possible to disseminate results to the patients.

Results

Recruitment

In total, 840 patients were recruited between 31st March 2016 and 14th December 2018. Seven patients in the intervention and four in the standard care group were either found to be ineligible

after randomisation or immediately withdrew consent leaving 415 and 414 analysable, respectively (Figure 2). Not all those recruited participated for 6 cycles of chemotherapy. Reasons for this varied but included: prescribed fewer than 6 cycles; chemotherapy discontinued, withdrew, or died. Most participants completed 4-6 cycles of chemotherapy (n = 723, 87.2%) before moving into the follow-up phase of the study (91.3%). Attrition was low and similar in both study arms; intervention (8.2%) and control (9.2%). Figure 2 provides details for the primary outcome (MSAS) noting numbers expected, numbers not collected/not analysable and numbers analysed.

Enrolment Characteristics

Randomisation achieved good balance between study arms in terms of age, gender, country, type of cancer and employment and educational status (though more in the intervention arm reported a higher degree). The mean age was 52.4 years (SD 12.2) and 81.8% were female. Breast cancer was the most common diagnosis (71.4%) and most were diagnosed with early stage disease stage I-II (53.4%). Highest numbers of participants were recruited from UK (31.7%) and Greece (31.2%). Half of the participants had no known co-morbidities. (see Table 1).

Adherence to the intervention

DCTAQ compliance was calculated for each patient, defined as the number of days on which at least one DCTAQ was completed divided by the number of days when a DCTAQ was available for completion, represented as a percentage. Participants were instructed to complete the DCTAQ every day but had the option to complete an additional DCTAQ at 'Anytime' if they felt their symptoms had worsened over the course of a day.

Compliance rates were calculated using the number of days which DCTAQs were completed, rather than the number of DCTAQs completed, as participants may have completed more than one per day, over-inflating compliance rates. DCTAQ compliance was high for the intervention group at 76.9% (DCTAQs completed =33,156, DCTAQs available for completion =43,118).

A total of 33,389 DCTAQs (33,156 daily DCTAQs and 233 Anytime DCTAQ) were completed. Of these, 3,456 generated a red alert and 3,746 generated an amber alert. Some of these alerts were 'linked' resulting in 3,389 (10.2%) linked red alerts and 3,649 (10.9%) linked amber alerts.

Primary Outcome

The total MSAS mean scores for the intervention and control groups at each assessment are shown in Table 2. For the intervention group, symptom burden remained at pre-chemotherapy treatment levels over all six chemotherapy cycles. In contrast, the control group reported an immediate increase in total symptom burden from cycle 1 (Table 2) which then slowly reduced over the five subsequent chemotherapy cycles. Using an identity link to give results on the original scale, the adjusted analysis least squares means on repeated measures were 0.36 in the intervention arm compared to 0.52 in the standard care arm giving a difference of -0.15 (95% CI -0.19 to-0.12, p <0.0001) in favour of the intervention (Table 3). This is equivalent to an ES = 0.5.

Separate analyses for the three MSAS subdomains (Table 3) showed that MSAS-GDI and MSAS-PSYCH mean scores decreased in both groups once chemotherapy treatment started. However, they were consistently lower in the intervention arm over the six chemotherapy cycles. The least squares mean was 0.46 in the intervention arm compared to 0.67 in the standard care arm giving a difference of -0.21 (95% CI -0.25 to -0.15, p<0.0001) for MSAS-

GDI (ES = 0.42). For MSAS-PSYCH, mean difference of -0.16 (95% CI -0.23 to -0.10, p<0.0001) and ES = 0.27. In contrast, MSAS-PHYS rose during chemotherapy but less so in the intervention arm (0.33 vs 0.54 with a difference of -0.21 (95% CI -0.26 to -0.17, p<0.0001)) in favour of the intervention and ES = 0.58.

In the adjusted analyses, both country and cancer type were related to PROM scores. MSAS scores were generally lower in patients with HD or NHL compared to breast or colorectal cancer. Moreover, UK MSAS scores tended to be similar to those from Norway and Ireland, while scores in Austria and Greece were significantly lower than the UK. However, subgroup analyses by country and type of cancer revealed that while benefits were found in all groups, the greatest intervention benefits were in patients with breast cancer, and HD and NHL in Austria, Ireland, and UK.

Secondary outcomes

FACT-G scores were higher in the intervention group than the standard care group across all cycles (Table 3) (Mean difference=4.06, 95% CI 2.65 to 5.46, p<0.0001). Similarly, a statistically significant between group mean difference was found on the following FACT-G domains in favour of the intervention group: physical (Mean difference = 1.75, 95% CI 1.25 to 2.25, p<0.0001) and functional (Mean difference =1.61, 95% CI 1.00 to 2.22, p <0.0001). The between group mean differences for the FACT-G emotional and social domains were not statistically significant.

Statistically significant between groups differences were found for mean scores for STAI-R trait anxiety (Table 3) (-1.15, 95% CI -1.86 to -0.44, p=0.002) and STAI-R state anxiety (-1.05, 95% CI -1.95 to -0.16, p = 0.020) in favour of the intervention group. The intervention group reported greater self-care self-efficacy than the standard care group (0.85, 95% CI 0.19 to 1.50, p = 0.011).

Supportive care needs tended to be lower for all the 5 SCNS-SF34 domains for the intervention group (Table 3). Psychological needs followed the same trend as MSAS with a sharp decrease once chemotherapy treatment started and with a larger decrease in the intervention arm. The largest observed benefits in the intervention arm were in relation to sexuality needs (-1.56, 95% CI -3.11 to -0.01, p = 0.048), patient care and support needs (-1.74 95% CI -3.31 to -0.16, p=0.03), and physical and daily living needs (-2.8, 95% CI -5.0 to -0.6, p = 0.013). No statistically significant differences were found in health system and information needs domain.

CASE-Cancer scores were higher for the intervention compared to the standard care group (0.81, 95% CI 0.19 to 1.43, p=0.010). The WLQ was completed by the 251 patients who were employed, and no significant differences were noted.

Adverse Events

Adverse events were generally balanced across the two groups. Three deaths occurred in each arm. Neutropenic events were higher in the intervention group (125 (63.8%) vs 71 (36.2%)) which was expected because the intervention was designed to detect and encourage clinicians to respond promptly. The numbers of planned (34 vs. 38) and unplanned hospitalisations (120 vs. 109) were similar in both groups (Table 4). No ASyMS device related incidents were reported

Discussion

To our knowledge, this large multicentre trial is the first to evaluate the efficacy of real time remote monitoring of chemotherapy-related side effects across more than one country and one of the first to focus mainly on those being treated with curative intent. Whilst we included people with metastatic Hodgkin's and non-Hodgkin's lymphomas in most of those cases, the purpose of the chemotherapy is still to achieve a cure. Overall, symptom burden remained at pre-treatment levels in patients who used ASyMS, whereas in our standard care group symptom burden increased rapidly from the start of chemotherapy treatment and remained high over the course of the RCT. Other studies of electronic symptom monitoring report similar findings, however these studies were conducted in a single country and health care system (Basch et al., 2016, Mooney et al., 2017, Denis et al., 2019, Absolom et al., 2021) Our results suggest that electronic approaches like ASyMS are likely effective across a range of health systems.

Greatest improvements were found for patients with breast cancer, HD or NHL in Austria, Ireland, and UK. While reasons for these differences are unclear, it may be that, as ASyMS was developed in the UK, it works best in health care systems that are most similar to the National Health Service (NHS) in terms of organisation and level of funding. However, it is not clear why symptom burden was higher in Norwegian participants. It may be that the number of patients from Norway was insufficient to show a difference between the intervention and control groups (Mooney et al., 2017, Fjell et al., 2020).

eSMART, in alignment with other studies, (Basch et al., 2016, Absolom et al., 2021) has reported changes in symptom burden over consecutive cycles of chemotherapy. Our findings suggest the benefits of remote monitoring begin within the first three cycles of chemotherapy and are sustained over time. Given that symptom burden is highest during earlier cycles of treatment and that symptoms gradually subside over the course of chemotherapy, this approach needs to be implemented in a pre-emptive fashion. Qualitative data from eSMART (to be published) indicates that contributory factors leading to reductions in symptoms burden include both anticipatory nature of the system and timely response by clinicians.

By convention, we considered that the larger the ES beyond the 0.25 cut-point, the stronger the indication is for a clinically important change in our primary outcome between intervention and control. From a clinical importance perspective, the mean between-group reduction of 0.15 in total MSAS scores was translated into an ES of 0.5 which is considered moderate according to Cohen's criteria (Cohen, 1988). This finding is promising and further substantiates our statistically significant results, pointing to a sizeable, positive, clinical impact on patients' symptom experience when self-reported symptoms were closely monitored via ASyMS. Our ES are either comparable or larger than ES previously reported in the relevant literature (Chang et al., 2004, Dapueto et al., 2014). Previously, in an RCT testing an interactive symptom-monitoring app during neoadjuvant chemotherapy for breast cancer, Fjell et al., (2020) reported an ES of 0.26 for between group total MSAS differences (and 0.34 for MSAS GDI scores) two weeks after the end of treatment. Effect sizes of 0.01-0.21 for between group MSAS GDI differences were reported in an RCT of computerised patient-reported symptom monitoring during weeks 1-4 of radiotherapy for various types of cancer (Fromme et al., 2016).

In addition to reduced symptom burden, the eSMART trial showed significant improvements in anxiety, HRQoL, self-efficacy, and supportive care needs in the intervention group. The improvements in overall HRQoL are consistent with findings from recent trials of proactive and intensified symptom management delivered using remote monitoring systems (Larson et al., 2017). While Basch et al. (2016) demonstrated similar results using the EQ5D, the five

dimensions of the EQ5D (i.e., mobility, self-care, usual activities, pain/discomfort, anxiety/depression) are assessed by a single item. We used validated PROM that comprehensively assess each of these outcomes and provide more detailed findings about the impact of remote monitoring systems on not only HRQoL but self-efficacy and supportive care needs. Whilst our findings suggest that our remote monitoring system has a broader impact, further analyses using techniques like parallel process growth modelling are required to evaluate concurrent changes in symptom burden and HRQoL outcomes.

eSMART is the first RCT in people with cancer to assess the impact of remote symptom monitoring on anxiety using a validated PROM. The ASyMS intervention was associated with statistically significant improvements in anxiety in the intervention group. Our findings may differ from relatively small post-intervention effects on psychological symptoms reported in the literature pertinent to the routine use of PROMs in cancer care (Kotronoulas et al., 2014); however, they are consistent with earlier studies of ASyMS in which patients reported feelings of enhanced safety and reassurance knowing that their symptoms were being remotely monitored and proactively managed (Maguire et al., 2014, McCall et al., 2008, McCann et al., 2009). Given that anxiety is the most common psychological symptom following a cancer diagnosis, is higher among people with cancer than the general population and is linked to poorer outcomes (Wang et al., 2020, Paterson et al., 2017), it may be postulated that these effects would benefit a large proportion of oncology patients, however this would need to be tested and confirmed in future studies.

Patients allocated to use ASyMS reported a statistically significant improvement in self-efficacy. Our findings are consistent with results from the eRAPID trial (Absolom et al., 2021). Daily symptom reporting with real time clinician support for moderate to severe symptoms and provision of tailored self-care information are novel features of ASyMS and are likely to promote the development of self-efficacy. Other remote monitoring systems that assess symptoms less frequently, for example weekly (Basch et al. 2016), may limit their potential to encourage patients to learn self-management strategies. Likewise, provision of real time support from clinicians may engender a greater sense of control. While other systems integrate symptom reports with the patient health record, they do not alert clinicians to contact patients within a pre-specified time period when symptoms are severe. Rather the onus remains on the patient to initiate contact with clinicians about severe symptoms. Recent research on neutropenic sepsis demonstrated patients are reluctant to report symptoms in a timely manner (Oakley et al., 2017).

The eSMART trial demonstrates that ASyMS can reduce supportive care needs in several domains during chemotherapy, including psychological, physical and daily living needs, patient care and support, and sexuality. The observed reductions may be partially explained by the significant reductions in anxiety and physical symptoms experienced by the intervention group. Daily reporting and feedback from clinicians may have been associated with the receipt of advice on coping with physical symptoms and side effects with a resultant decrease in physical and daily living needs. This enhanced symptom support may have resulted in patients perceiving that their clinicians were more sensitive to their needs and decreased their need for various aspects of supportive care.

Given that sexuality needs are often overlooked during cancer and chemotherapy treatment (Ben Charif et al., 2016, O'Connor et al., 2019), it may be that the comprehensive e-library of useful resources that included information on sexual wellbeing was a non-threatening and easily accessible source of information, accordingly, reducing needs in this domain.

Furthermore, because patients in the intervention arm had reduced symptom burden, reduced anxiety, and better HRQoL, they may have been more inclined to engage in sexual activity. The lack of significant change in health systems and information needs domain may be explained by the limited resources on this topic in the ASyMS e-library. Future research should explore patients' perceptions of what other additional information needs to be included in the e-library to optimise use and impact this outcome.

An evaluation of work limitations was an important component of this RCT given the interruptions in employment associated with cancer treatment (Dumas et al., 2020, van Muijen et al., 2017). Work limitation scores were not statistically significantly different between intervention and control group. This finding is not consistent with a previous study (Tevaarwerk et al., 2017) who reported significant work limitations in patients undergoing curative chemotherapy. However, our results should be interpreted with caution because only those patients who were working completed this PROM and the number was small.

Compliance with the intervention was very good (76.9%) and compares favourably with similar studies reporting slightly lower compliance rates (Basch et al. 2016, (Absolom et al., 2021), especially given that eSMART required daily symptom reporting which some may consider onerous. It is likely that, in our study, compliance was positively influenced not only by clinical staff's enthusiasm and motivation towards the study in general but also by participants' experiences of the intervention 'at work'. Qualitative data, to be reported in future publications, demonstrates that participants appreciated the reassurance of knowing clinical staff were being alerted to symptoms of clinical concern and would respond appropriately. Likewise, clinicians' experiences with the system positively reinforced their attitudes towards it.

Importantly, our RCT found that the safety of the ASyMS system was satisfactory with no device-related incidents reported. Adverse events were balanced between the two trial arms, with three reported deaths in each arm and similar rates of hospitalisation. However, this result is not surprising as hospital admission rates in this population are relatively low. The incidence of neutropenic events was higher in the intervention arm. However, this finding was expected because of the remote monitoring and early identification of neutropenic fever and associated symptoms.

Approximately 30% of patients approached declined to participate. While 27% who declined did not give a reason for their decision, those who did mainly cited the psychological impact of diagnosis and lack of confidence with technology as their rationale. Our refusal rate is similar to comparable studies that recruited high numbers of participants being treated with curative intent (Absolom et al 2021) and higher than those who recruited patients with advanced disease (Basch et al 2016), although data collection in the latter study was less onerous being weekly via email or in clinic. Anecdotally, clinicians in this study reported that the intensity of the study at a time when people were feeling stressed was a frequently voiced concern of those potential participants who declined to take part. However, the high adherence rate related to the completion of the DCTAQ by patients randomised to the intervention demonstrate a positive indicator of the usability and adoption of ASyMS by patients within the context of their daily routines during their chemotherapy experiences.

Conclusion

The results of the eSMART study suggest that ASyMS is an effective intervention for reducing patient symptom burden and improving HRQoL during adjuvant chemotherapy treatment across a range of cancer types. The use of ASyMS was associated with significant reductions in anxiety and improvements in several important domains of supportive care needs and self-efficacy. Moreover, our results were consistent across five European countries, although perhaps with greater impact in Austria, Republic of Ireland, and UK. Our success in implementing ASyMS across several diverse health systems suggests that our system can be easily scaled up and adapted for use in various international settings.

Moving forward, advancing the state of the art of symptom management by using systems like ASyMS is vital. Future versions should harness the power of artificial intelligence coupled with the use of real-world data to develop more predictive, personalised, and targeted interventions. These approaches are likely to lead to improvements in patient outcomes and efficiencies in care. Advancing the state of the art will entail the evaluation of the efficacy of remote symptom monitoring and managing systems like ASyMS with other treatment modalities (e.g., targeted therapies or oral anticancer treatment). The ultimate vision is to have a multimodal seamless system of remote symptom monitoring that is used at the initiation of treatment and continues to be used throughout the cancer pathway.

Our findings have relevance when considered in the context of the COVID-19 pandemic. With the cancer community facing unprecedented challenges in the delivery of chemotherapy (Al-Shamsi et al., 2020), ASyMS can provide a safe, secure and 'real-time' system of care that optimises symptom management and supports patients to remain at home. Importantly, the system can expedite informed and appropriate referrals to primary and secondary clinicians as needed. Furthermore, in terms of workforce needs and cost containment (Mayor 2020), ASyMS enables clinicians to care for multiple patients at once – using virtual lines of communication to deliver high quality and safe care at a distance.

Strengths and Limitations

This is the largest trial to date of remote monitoring and management of symptoms during chemotherapy for cancers being treated with curative intent. Although we recruited people with HD and NHL with metastatic disease, in most of those cases, the intent of chemotherapy was still curative. Further strengths of this study include its robust randomised controlled design, the fully powered sample size, longitudinal assessments of symptoms and outcomes and multi-diagnosis, multi-site and multi-country deployment of a real-time remote patient monitoring intervention. Our study, therefore, addressed many of the limitations of previous evaluations of remote monitoring technologies that tend to be deployed in single sites and recruit patients from a single diagnostic group. Our overall attrition rate was much lower than expected and comparable with similar studies (Basch et al. 2016, Absolom et al. 2021) demonstrating external validity and high acceptability of the intervention to patients and clinicians.

A limitation of our study is that almost three-quarters of participants had breast cancer and were female. This is a common limitation of supportive cancer care research and reflects the high incidence of breast cancer in Europe. Careful consideration was given before permitting clinical sites to recruit increased numbers of patients with breast cancer than originally intended, but it was judged more important that the study achieved power than the proposed diagnostic breakdown without power. It may be argued that this limits the generalisability of our findings to the wider cancer patient population. However, having similar results with patients with colorectal cancer suggest that it could be beneficial in this cancer. Considering the relatively

small number of recruited patients with HD or NHL, a larger study is warranted to evaluate the benefits of this system in this patient group. Future research may also expand to focus on other diagnostic groups. Seven patients were excluded after randomisation, but the associated bias was reduced because numbers were equally distributed between the intervention and standard care arms. Although patients and clinicians were aware of the allocation of the study intervention, the trial statisticians were blinded throughout the analysis. Lastly, due to unprecedented technical challenges encountered across all sites concerning the connectivity of ASyMS SIM cards, patients in the intervention arm were asked to revert to standard care for a period of approximately 2 weeks to ensure patient safety whilst technical problems were being fixed. Technical testing indicated that this occurrence was not related to the ASyMS device. This event may therefore have impacted on the overall eSMART trial results.

Implications for clinicians and for policy

The results of the eSMART trial support the use of remote symptom monitoring in routine care for patients treated with curative intent. When considered with findings of comparable RCTs (Basch et al., 2016, Mooney et al., 2017, Velikova et al., 2020), our results support the incorporation of remote symptom monitoring as gold standard into evidence-based guidelines on the assessment and management of symptoms in patients with cancer. Government and health organisations are increasingly responding to the rapidly evolving digital health landscape to provide optimal services and care – even more so in response to the COVID-19 global pandemic – and so they collectively recognise ways in which digital health technologies can and are disrupting the status quo (Whitelaw et al., 2020). Many of these governmental digital health policies prioritise citizen empowerment, enhanced self-management and digitally enabled access to services (European Commission 2018). Our findings suggest that an evidence-based remote monitoring intervention, such as ASyMS, has real potential to be implemented into routine care and make a meaningful difference in a variety of cancer patient populations.

Acknowledgements

We thank the participants across our partner European countries and hospital sites for taking part in eSMART. We also extend our thanks to the professionals at the participating clinical sites (Medical University Vienna Comprehensive Cancer Centre, Austria; Agioi Anargiri Cancer Hospital, Greece; Metropolitan Hospital, Greece; Air Force General Hospital, Greece; St James' Hospital, Ireland; St Vincent's Private Hospital, Ireland; St Vincent's University Hospital, Ireland; Innlandet Hospital Trust Division Gjøvik-Lillehammer, Norway; Guy's and St Thomas' NHS Foundation Trust, UK; Mount Vernon Cancer Centre, UK; St George's Healthcare Trust, UK; and University College London Hospitals, UK) for all their hard work and dedication to the trial. We also thank the Data Monitoring Committee and various researchers and members of the respective eSMART partners for their dedicated efforts to this 5-year project.

Contributions

RM, LM, GK, NK, ER. JA, PF, EP, EF, PF, AG, PMcC, GB, CM, DO, AF, SK, PD obtained funding for the research. All authors contributed to either the design or conduct of the study. NDS performed the statistical analyses supervised by PD. The first draft of this manuscript was produced by RM, PD and LM and all authors reviewed, edited, and approved the final version. RM and PD are the guarantors of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria were omitted.

Funding

This trial was funded by the European Commission (EC) via the FP7-HEALTH-2013-INNOVATION-1 grant award scheme, grant award number 602289. The trial was sponsored by the University of Strathclyde. The views expressed in this article are those of the authors and not necessarily those of the EC or the University of Strathclyde. The funders and the sponsors of the trial had no role in the design, undertaking, and reporting of the study. The funders received status reports.

Competing Interests

Grant funding for research but no other competing interest: All authors completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from the European Commission for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Ethical Approval

The study was approved by NHS Lothian South East Scotland Research Ethics Committee 02, Reference Number 14/SS/1062. The study received local clinical site Ethical approvals in each partner country prior to commencing. The trial is registered on *ClinicalTrials.gov* (NCT02356081).

Data Sharing

The study protocol was published previously. Data will not be released to any external parties for the first 12 months following publication of this manuscript. Following this time, requests for access to de-identified individual participant data that underlie the results reported in this article should be addressed to the corresponding author and should include clear and specified plans of how the data is to be used. All proposals for data use will need approval of the co-authors consortium partner leads before any data are released.

Transparency

The manuscript guarantors (RM, PD) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study were omitted and any deviations from the original study plan were explained.

Summary boxes

What is already known about this topic
Effective symptom monitoring and management is essential during chemotherapy treatment for cancer. Current approaches for reporting symptoms rely on patient retrospective recall and self-identification of severe symptoms to prompt contact with their clinicians. Digital remote monitoring interventions to support patients during chemotherapy are available but very few were evaluated in cancers being treated with curative intent.
What this study adds
ASyMS is an effective intervention for reducing symptom burden and improving quality of life during adjuvant chemotherapy for people with breast cancer, colorectal cancer, Hodgkin's Disease and Non-Hodgkin's lymphoma. ASyMS impacts positively on a range of additional important patient outcomes during chemotherapy, including anxiety and self-efficacy. Digital solutions for remote monitoring and managing of chemotherapy symptoms – like ASyMS - can be delivered across multiple sites in European Countries with diverse healthcare systems.

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Table 1: Participant characteristics at enrolment

Variables		All patients	Intervention	Standard care
N		829	415	414
Age, mean (SD)		52.4 (12.2)	51.9 (12.4)	52.9 (12.1)
Gender, n (%)	Male	151 (18.2)	75 (18.1)	76 (18.4)
	Female	678 (81.8)	340 (81.9)	338 (81.6)
Marital status, n (%)	Married	553 (66.7)	273 (65.8)	280 (67.6)
	Single	129 (15.6)	68 (16.4)	61 (14.7)
	Divorced	87 (10.5)	45 (10.8)	42 (10.1)
	Widowed	38 (4.6)	14 (3.4)	24 (5.8)
	Not known	22 (2.7)	15 (3.6)	7 (1.7)
Education, n (%)	Primary	60 (7.3)	30 (7.4)	30 (7.3)
	Secondary	318 (38.9)	141 (34.7)	177 (43.1)
	University	439 (53.7)	235 (57.9)	204 (49.6)
Employment, n (%)	Full time	375 (45.2)	192 (46.3)	183 (44.2)
	Part time	109 (13.2)	53 (12.8)	56 (13.5)
	Home maker	82 (9.9)	40 (9.6)	42 (10.1)
	Unemployed	67 (8.1)	34 (8.2)	33 (8.0)
	Retired	173 (20.9)	82 (19.8)	91 (22.0)
	Rather not say	23 (2.8)	14 (3.4)	9 (2.2)
Smoking, n (%)	Never	414 (49.9)	214 (51.6)	200 (48.3)
	Ex-smoker	280 (33.8)	133 (32.1)	147 (35.5)
	Not everyday	38 (4.6)	16 (3.9)	22 (5.3)
	Everyday	97 (11.7)	52 (12.5)	45 (10.9)
Alcohol consumption, n (%)	Every Day	32 (3.9)	18 (4.3)	14 (3.4)
	Occasionally	593 (71.5)	306 (73.7)	287 (69.3)
	Never	204 (24.6)	91 (21.9)	113 (27.3)
Country, n (%)	Austria	140 (16.9)	71 (17.1)	69 (16.7)
	Greece	259 (31.2)	127 (30.6)	132 (31.9)
	Ireland	135 (16.3)	68 (16.4)	67 (16.2)
	Norway	32 (3.9)	16 (3.9)	16 (3.9)
	UK	263 (31.7)	133 (32.0)	130 (31.4)
No. of co-morbidities n (%)	0	420 (50.7)	220 (53.0)	200 (48.3)
	1-4	393 (47.4)	188 (45.3)	205 (49.5)
	5+	16 (1.9)	7 (1.7)	9 (2.2)
Cancer type, n (%)	Breast	592 (71.4)	297 (71.6)	295 (71.3)
	Colorectal	152 (18.3)	74 (17.8)	78 (18.8)
	Hodgkin's lymphoma	26 (3.1)	14 (3.4)	12 (2.9)
	Non-Hodgkin lymphoma	59 (7.1)	30 (7.2)	29 (7.0)
Staging***, n (%)	Stage 0	3 (0.4)	2 (0.5)	1 (0.2)
	Stage I	129 (15.6)	63 (15.2)	66 (15.9)
	Stage II	310 (37.4)	154 (37.1)	156 (37.7)
	Stage III	310 (37.4)	157 (37.8)	153 (37.0)
	Stage IV*	21 (2.5)	10 (2.4)	11 (2.7)
	Undefined**	56 (6.8)	29 (7.0)	27 (6.5)
Chemotherapy	1	3 (0.4)	3 (0.7)	0

cycles, n (%)	2	4 (0.5)	3 (0.7)	1 (0.2)
	3	19 (2.3)	12 (2.9)	7 (1.7)
	4	192 (23.2)	95 (22.9)	97 (23.4)
	5	27 (3.3)	14 (3.4)	13 (3.1)
	6	504 (60.8)	248 (59.8)	256 (61.8)
	7‡	10 (1.2)	8 (1.9)	2 (0.5)
	8‡	65 (7.8)	30 (7.2)	35 (8.5)
	12‡	5 (0.6)	2 (0.5)	3 (0.7)
No. of chemotherapy cycles, median (range)		6 (1,12)	6 (1,12)	6 (2,12)

Notes:
* Stage IV was not an exclusion criterion for participants with haematological cancer.
** Data not captured at clinical site before end of trial.
*** TNM/UICC system for breast/colorectal cancer; Ann Arbor Staging System for haematological cancers.
‡ Until a substantial amendment to the study protocol was made to limit patient participation to up to six chemotherapy cycles, the first 80 patients enrolled in the trial participated until the end of their prescribed chemotherapy protocol, and therefore show as having completed more than six cycles.
Abbreviations: SD - Standard deviation

Table 2: Descriptive Summary of Primary Outcome – Total MSAS and Sub-domains

Total MSAS	Intervention			Standard Care		
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
Baseline	407	0.35 (0.30)	0.27 (0, 1.62)	393	0.39 (0.31)	0.32 (0, 1.94)
Cycle 1	367	0.33 (0.27)	0.25 (0, 1.35)	340	0.51 (0.42)	0.40 (0, 2.50)
Cycle 2	360	0.35 (0.28)	0.28 (0, 1.98)	334	0.53 (0.40)	0.44 (0, 2.25)
Cycle 3	343	0.35 (0.31)	0.28 (0, 1.45)	320	0.52 (0.44)	0.43 (0, 3.24)
Cycle 4	304	0.37 (0.31)	0.31 (0, 1.62)	280	0.53 (0.44)	0.45 (0, 3.04)
Cycle 5	246	0.34 (0.29)	0.27 (0, 1.45)	229	0.52 (0.41)	0.44 (0, 2.22)
Cycle 6	179	0.37 (0.28)	0.30 (0, 1.39)	157	0.48 (0.39)	0.38 (0, 1.88)
MSAS GDI						
Baseline	406	0.66 (0.55)	0.56 (0. 3.24)	393	0.73 (0.55)	0.60 (0, 3.36)
Cycle 1	366	0.42 (0.47)	0.25 (0, 2.36)	337	0.66 (0.62)	0.48 (0, 3.14)
Cycle 2	361	0.42 (0.46)	0.28 (0, 3.08)	334	0.67 (0.61)	0.51 (0, 3.12)
Cycle 3	343	0.44 (0.49)	0.28 (0, 2.46)	318	0.70 (0.64)	0.56 (0, 3.48)
Cycle 4	304	0.46 (0.46)	0.32 (0, 2.18)	277	0.69 (0.65)	0.56 (0, 3.58)
Cycle 5	246	0.42 (0.49)	0.27 (0, 2.40)	227	0.67 (0.57)	0.56 (0, 2.68)
Cycle 6	179	0.44 (0.46)	0.32 (0, 2.46)	157	0.62 (0.58)	0.44 (0, 2.80)
MSAS PSYC						
Baseline	400	0.90 (0.80)	0.67 (0, 3.57)	388	1.00 (0.77)	0.84 (0, 3.83)
Cycle 1	365	0.48 (0.60)	0.26 (0, 3.08)	340	0.72 (0.74)	0.51 (0, 3.90)
Cycle 2	359	0.46 (0.55)	0.31 (0, 3.69)	334	0.68 (0.74)	0.46 (0, 3.23)
Cycle 3	343	0.47 (0.61)	0.26 (0, 3.07)	323	0.67 (0.74)	0.46 (0, 3.74)
Cycle 4	304	0.51 (0.57)	0.31 (0, 2.62)	280	0.69 (0.75)	0.46 (0, 3.57)
Cycle 5	246	0.48 (0.64)	0.26 (0, 3.59)	231	0.65 (0.69)	0.46 (0, 3.46)
Cycle 6	179	0.52 (0.62)	0.31 (0, 2.71)	157	0.64 (0.68)	0.51 (0, 3.83)
MSAS PHYS						
Baseline	406	0.27 (0.35)	0.15 (0, 2.10)	395	0.31 (0.36)	0.20 (0, 1.97)
Cycle 1	365	0.27 (0.31)	0.17 (0, 1.54)	338	0.51 (0.47)	0.38 (0, 2.36)
Cycle 2	360	0.31 (0.37)	0.19 (0, 2.19)	336	0.54 (0.46)	0.46 (0, 2.66)
Cycle 3	344	0.34 (0.38)	0.24 (0, 2.07)	319	0.56 (0.50)	0.48 (0, 3.28)
Cycle 4	305	0.35 (0.36)	0.25 (0, 2.01)	280	0.57 (0.51)	0.47 (0, 2.97)
Cycle 5	247	0.32 (0.34)	0.20 (0, 1.51)	226	0.56 (0.47)	0.43 (0, 2.26)
Cycle 6	179	0.34 (0.33)	0.26 (0, 1.71)	157	0.49 (0.45)	0.38 (0, 2.01)

Table 3: Mixed model, repeated measures analysis of change from baseline using Gamma model

	Adjusted* LS Means (95% CI)		Adjusted* mean difference (95% CI)	
Variable	**Intervention**	**Standard Care**	**Intervention v. Standard care**	**p-value**
Total MSAS**	0.36 (0.34 to 0.39	0.52 (0.49 to 0.54)	-0.15 (-0.19 to -0.12)	<0.0001
MSAS-GDI	0.46 (0.42 to 0.50)	0.67 (0.63 to 0.71)	-0.21 (-0.27 to -0.16)	<0.0001
MSAS-PSYC	0.51 (0.46 to 0.55)	0.67 (0.63 to 0.72)	-0.16 (-0.23 to -0.10)	<0.0001
MSAS-PHYS	0.33 (0.30 to 0.36)	0.54 (0.51 to 0.58)	-0.21 (-0.26 to -0.17)	<0.0001
FACT-G Total	86.3 (85.3 to 87.3)	82.3 (81.3 to 83.3)	4.06 (2.65 to 5.46)	<0.0001
FACT-G Physical	23.4 (21.3 to 23.7)	21.6 (21.3 to 22.0)	1.75 (1.25 to 2.25)	<0.0001
FACT-G Emotional	20.4 (20.2 to 20.7)	19.9 (19.6 to 20.1)	-0.54 (-1.23 to 0.16)	0.129
FACT-G Social	23.6 (23.2 to 23.9)	23.2 (22.8 to 23.5)	0.44 (-0.06 to 0.93)	0.082
FACT-G Functional	19.1 (18.7 to 19.5)	17.5 (17.1 to 17.9)	1.61 (1.00 to 2.22)	<0.0001
STAI-Trait	32.7 (32.2 to 33.3)	33.9 (33.4 to 34.4)	-1.15 (-1.90 to -0.41)	0.003
STAI-State	31.9 (31.2 to 32.6)	33.0 (32.4 to 33.7)	-1.13 (-2.06 to -0.20)	0.017
CASE-Cancer	43.7 (43.3 to 44.2)	42.9 (42.3 to 43.4)	0.81 (0.19 to 1.43)	0.010
SCNS-SF34 Psychological	23.2 (21.9 to 24.6)	24.4 (23.0 to 25.8)	-1.14 (-3.04 to 0.75)	0.236
SCNS-SF34 Health System & Information	22.3 (21.1 to 23.4)	23.7 (22.5 to 24.9)	-1.46 (-3.13 to 0.21)	0.087
SCNS-SF34 Sexuality needs	12.0 (10.9 to13.1)	13.5 (12.4 to 14.7)	-1.56 (-3.11 to -0.01)	0.048
SCNS-SF34 Patient care and support	17.5 (16.5 to 18.6)	19.3 (18.1 to 20.4)	-1.74 (-3.31 to -0.16)	0.03
SCNS-SF34 Physical & daily living	27.3 (25.7 to 28.8)	30.0 (28.5 to 31.6)	-2.8 (-5.0 to -0.6)	0.013

*Adjusted for Baseline PROM, cycle, age, gender, cancer type, co-morbidity, country
** Primary outcome.

Table 4: Table of Adverse events

Adverse event	All patients n	Intervention n (%)	Normal Care n (%)
Deaths [1]	6	3 (50.0)	3 (50.0)
Neutropenic sepsis events [2]	196	125 (63.8)	71 (36.2)
Planned hospital admissions [2]	72	34 (47.2)	38 (52.8)
Unplanned hospital admissions [2]	229	120 (52.4)	109 (47.6)

[1] Collected in Promasys

[2] Collected in case note reviews

CLINICAL STUDY PROTOCOL

TITLE

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

Protocol Status: **Final**

Version Number: **Version 1.7**

Date: **160617**

Confidentiality Statement

1 STUDY PROTOCOL AGREEMENT FORM

Authorisation of final version

Study Title

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

On behalf of the Sponsor (University of Strathclyde):

Job Title:

Signature …… Date ……

Name:

Principal Investigator Agreement

I agree to conduct this study (i.e. eSMART) according to this protocol and to comply with its requirements, subject to ethical principles that have their origins in the Declaration of Helsinki.

I will promptly submit the protocol to applicable ethical review board(s). I agree not to make any changes to the protocol without agreement from the sponsor and prior review and written approval from the local Ethics Committee, except where necessary to halt an immediate threat to subject safety, or for administrative study details when such actions are permitted by local regulations.

I will make certain that all personnel assisting with the study will be adequately informed about the investigational device and their study-related duties as described in the protocol.

I understand that, should the decision be made by the Sponsor to terminate prematurely or suspend the study, at any time and for whatever reason, such decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate immediately in writing to the Sponsor or their representatives.

Principal Investigator

Signature …… Date ……

Name:

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ASCO	American Society of Clinical Oncology
ASyMS	Advanced Symptom Management System
CA	Competent Authority
CASE-Cancer	Communication and Attitudinal Self-Efficacy scale for cancer
CRC	Clinical Research Centre
(e)CRF	(electronic) Case Report Form
CSRI	Client Services Receipt Inventory
CTU	Clinical Trials Unit
DESCA	Development of a Simplified Consortium Agreement
DMC	Data Monitoring Committee
ECPC	European Cancer Patient Coalition
EQ-5D	EuroQol 5-Dimensions
eSMART	electronic Symptom Management using the Advanced Symptom Management System (ASyMS) Remote Technology
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy-General
FHMS	Faculty of Health and Medical Sciences
FP7	7th Framework Programme
FSN	Field Safety Notice
GCP	Good Clinical Practice
GP	General Practitioner
HD	Hodgkin's disease
HR-QoL	Health-related Quality of Life
HOQS	Head of Operations and Quality Systems
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ISO	International Organisation for Standardisation
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IT	Information Technology
MAR	Missing-at-Random
MASCC	Multinational Association for Supportive Care in Cancer
MSAS	Memorial Symptom Assessment Scale
NCA	National Competent Authority
NHL	non-Hodgkin lymphoma
NHS	National Health Service
PI	Principal Investigator
PRM	Predictive Risk Model
(e)PROM	(electronic) Patient-Reported Outcome Measure
QALY	Quality-Adjusted Life Years

Abbreviation	Definition
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAP	Statistical Analysis Plan
SOPs	Standard Operating Procedures
SCNS-SF34	Supportive Care Needs Survey-Short Form 34
Surrey CRC	Surrey Clinical Research Centre
Wi-Fi	Wireless Fidelity
WLQ	Work Limitations Questionnaire

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5 PROTOCOL SYNOPSIS

Title	eSMART: Randomised controlled trial to evaluate electronic Symptom Management using the Advanced Symptom Management System (ASyMS) Remote Technology for patients with cancers
Sponsor	University of Strathclyde
Principal Investigator	Professor Roma Maguire, University of Strathclyde
Study Location	Multi-national
Indication	Breast Cancer, Colorectal Cancer, Haematological Cancer (Hodgkin's Disease [HD] or Non-Hodgkin Lymphoma [NHL])
Study Objectives Primary:	Part 1: ▪ Review the literature and international/national/local guidelines for the assessment and management of chemotherapy-related toxicity to ensure that ASyMS reflects local and current practice. ▪ Refine risk algorithms for symptom alerts based on review of guidelines and local practice, and patient and clinician feedback. ▪ Standardise response to symptom alerts across European sites. ▪ Prepare the participating clinical sites for the application of ASyMS through assessment of infrastructure and human and material resource requirements. ▪ Translate and linguistically validate the assessment questionnaires (where appropriate) into the required languages for the participating sites. ▪ Translate all additional study components into the required languages. ▪ Feasibility testing and assessment of the technological readiness of the ASyMS system at the participating sites in preparation for Part 2. Part 2: To evaluate via a repeated measures, parallel group, stratified randomised controlled trial (RCT), the short- and long-term impact of the ASyMS intervention (a remote patient-monitoring system to monitor and manage the toxicities of cancer treatment), on symptom burden (total MSAS scores) in people with breast, colorectal or haematological cancers (i.e. HD or NHL) receiving chemotherapy for the first time.
Secondary:	Part 2: To evaluate the short and long-term impact of the ASyMS intervention on quality of life, supportive care needs, (state, trait) anxiety, self- efficacy and work limitations. To evaluate the cost-effectiveness and changes in clinical practice as a result of the implementation of ASyMS in different European healthcare settings.
Exploratory:	Part 2: To develop and test Predictive Risk Models (PRMs) (utilising data from previous studies and generated through the Part 2 trial) to

	predict chemotherapy-related toxicity in patients with breast, colorectal or haematological cancers (HD or NHL).
Study Design	Two-part, pragmatic, multinational study Part 1. (a) Preparatory work, involving systematic literature reviews, algorithm refinement and patient/clinician advisory group discussions. (b) Feasibility testing period, as a single-arm, prospective observational study. Part 2. Repeated measures, parallel-group stratified RCT.
Population	Patients diagnosed with breast, colorectal or haematological cancers (HD or NHL) receiving (Part 1) or scheduled to receive (Part 1 and Part 2) chemotherapy for the first time.
Main Selection Criteria	Part 1 (Feasibility Testing). Required patient sample size: *n*=2 per diagnostic group per participating site (i.e. max. *n*=6 per participating site depending on the different cancer types being evaluated at each site). Required professional sample size: *n*≤20 per participating site (Assessment of changes in clinical practice questionnaire). Eligibility criteria: Part 1 (Feasibility Testing): Patient Sample Required patient sample size: *n* ≤6 per participating site Inclusion criteria ▪ Adults (≥18 years). ▪ Diagnosed with breast cancer, colorectal cancer, or a haematological malignancy (i.e. Hodgkins Disease or Non-Hodgkins Lymphoma). ▪ Scheduled to start chemotherapy treatment for the first time, or (if previous chemotherapy has been received), scheduled to receive chemotherapy for the first time in the last 5 years (however patients who have received neoadjuvant chemoradiation for colorectal cancer **are** eligible for inclusion). ▪ Scheduled to receive a 2-, 3- or 4-weekly chemotherapy treatment, i.e. chemotherapy administered in repeated cycles of 14, 21 or 28 days, respectively. ▪ Scheduled to receive a minimum of 3 cycles of chemotherapy treatment. ▪ Physically/psychologically fit to participate in the study as confirmed by a member of the patient's multidisciplinary care team. ▪ Able to read, understand and write in the respective language. Exclusion criteria: ▪ Patients with breast cancer or colorectal cancer with a distant metastasis, i.e. stage IV disease as defined by the TNM/UICC, (at the start of their chemotherapy treatment). ▪ Patients with a haematological malignancy (HD or NHL), who have B symptoms, (at the start of their chemotherapy treatment).

	▪ Scheduled to receive concurrent radiotherapy at any point over the planned course of chemotherapy treatment. ▪ Scheduled to receive weekly chemotherapy treatment ▪ Diagnosed with the same type of cancer (i.e. where relapse has occurred) AND/OR another type of cancer (the only exception non-melanoma skin cancer) within the 5 years prior to recruitment to the study. ▪ Received chemotherapy treatment for any medical reason within the last 5 years (unless this is neoadjuvant chemoradiation for colorectal cancer). ▪ Unable to provide written informed consent. Professional Sample Required professional sample size: *n*≤20 per participating site (Assessment of Changes in Clinical Practice Questionnaire) ▪ Adults (≥18 years). ▪ Involved in the delivery of care or data monitoring of people with breast cancer, colorectal cancer, or haematological malignancies (i.e. HD or NHL). ▪ Able to provide informed consent Part 2 (RCT: Intervention and Follow Up Phases) (all patients will be enrolled for the follow-up phase unless they withdraw): Patient Sample Required patient sample size: *n*=1,108 in total. Inclusion criteria ▪ Adults (≥18 years). ▪ Diagnosed with breast cancer, colorectal cancer, or a haematological malignancy (i.e. Hodgkins Disease or Non-Hodgkins Lymphoma). ▪ Scheduled to start chemotherapy treatment for the first time, or (if previous chemotherapy has been received), scheduled to receive chemotherapy for the first time in the last 5 years (however patients who have received neoadjuvant chemoradiation for colorectal cancer **are** eligible for inclusion). ▪ Scheduled to receive a 2-, 3- or 4-weekly chemotherapy treatment, i.e. chemotherapy administered in repeated cycles of 14, 21 or 28 days, respectively. ▪ Scheduled to receive a minimum of 3 cycles of chemotherapy treatment. ▪ Physically/psychologically fit to participate in the study as confirmed by a member of the patient's multidisciplinary care team. ▪ Able to read, understand and write in the respective language. Exclusion criteria {RCT: Intervention Phase (all patients will be enrolled for the follow-up phase unless they withdraw): ▪ Patients with breast cancer or colorectal cancer with a distant metastasis, i.e. stage IV disease as defined by the TNM/UICC (at the start of their chemotherapy treatment). ▪ Patients with a haematological malignancy (HD or NHL), who have B symptoms, (at the start of their chemotherapy treatment).

	▪ Scheduled to receive concurrent radiotherapy at any point over the planned course of chemotherapy treatment. ▪ Scheduled to receive weekly chemotherapy treatment ▪ Diagnosed with the same type of cancer (i.e. where relapse has occurred) AND/OR another type of cancer (the only exception non-melanoma skin cancer) within the 5 years prior to recruitment to the study. ▪ Received chemotherapy treatment for any medical reason within the last 5 years (unless this is neoadjuvant chemoradiation for colorectal cancer). ▪ Unable to provide written informed consent. Professional Sample Required clinician sample size: $n \leq 20$ per participating site (Assessment of Changes in Clinical Practice Questionnaire and telephone/face-to-face interviews/focus groups) ▪ Adults (≥18 years). ▪ Involved in the delivery of care or data monitoring of people with breast cancer, colorectal cancer, or haematological malignancies (i.e. HD or NHL). ▪ Able to provide informed consent
Concurrent Controls	Part 2. RCT (Intervention and Follow Up Phases) Patients diagnosed with breast cancer, colorectal cancer, or haematological cancers (HD or NHL) receiving standard care as per the participating site's care protocols.
Study Endpoints	Part 1. ▪ Literature and international/national/local guidelines for the assessment and management of chemotherapy-related toxicity systematically and fully reviewed. ▪ Risk algorithms for symptom alerts refined based on review of guidelines and local practice, and patient and clinician feedback. ▪ Response to symptom alerts standardised across European sites. ▪ Successful feasibility testing and technological readiness demonstrated of the ASyMS intervention at the participating sites in preparation for Part 2. ▪ Assessment questionnaires translated and linguistically validated (where appropriate) into the required languages. Part 2. Primary: ▪ Reduction in patient symptom burden (total MSAS scores) during chemotherapy (up to 6 cycles), compared to standard care, as evidenced by statistically significantly lower total MSAS scores (primary outcome) over CTx after adjusting for baseline scores (total sample, subgroups according to type of diagnosis, subgroups according to country).
	Part 2. Secondary: ▪ Reduction in patient symptom burden (total MSAS scores) up to one-year post-intervention follow-up, compared to standard care, as evidenced by statistically significantly lower total MSAS scores at pre-specified time-points and during the one-year period thereafter (total sample, subgroups according to type of diagnosis, subgroups according to country).

	▪ Reduction in symptom burden (total MSAS score) at mid-CTx3 (i.e. peak symptom burden), compared to standard care, as evidenced by statistically significantly lower total MSAS scores. ▪ Increase in patient overall HR-QoL and HR-QoL domain scores (FACT-G scores) during active chemotherapy and during the one-year post-intervention follow-up thereafter (total sample, subgroups according to type of diagnosis, subgroups according to country). ▪ Reduction in patient overall supportive care needs, state/trait anxiety and domains of need during active chemotherapy and during the one-year post-intervention follow-up (SCNS-SF34 total and subscale scores) compared to standard care adjusting for baseline scores (total sample, subgroups according to type of diagnosis, subgroups according to country). ▪ Improvement in patient self-efficacy (total CASE-Cancer scores) during active chemotherapy and during the one-year post- intervention follow-up compared to standard care adjusting for baseline scores (total sample, subgroups according to type of diagnosis, subgroups according to country). ▪ Fewer work limitations (total WLQ scores) during active chemotherapy and during the one-year post-intervention follow-up compared to standard care adjusting for baseline scores (total sample, subgroups according to type of diagnosis, subgroups according to country). ▪ Health system costs of the ASyMS intervention (total sample and country-specific). ▪ Positive changes in clinical practice as a result of the ASyMS intervention (site/country-specific).
	Exploratory endpoint: ▪ Successful development and testing of PRMs for the prediction of study outcomes in patients with breast, colorectal or haematological cancers.
Parameters of Effectiveness	<u>Feasibility Parameters (Part 1)</u> A number of parameters will be evaluated focusing on the technological readiness of the ASyMS intervention for use in Part 2: ▪ Training of patients/staff to use ASyMS ▪ Registration of patients and clinicians on ASyMS ▪ Use of patient handset (completion of symptom questionnaire, access to self-care, access to symptom graphs, library, useful contacts) ▪ Transfer of data from patient handset to study server ▪ Clinician access and log onto the ASyMS web-portal ▪ Ability of clinicians to deal with an alert using the ASyMS web portal ▪ Ability of clinicians to log on and use ASyMS nurse handset for the receipt of alerts ▪ Technological connectivity of ASyMS (mobile connectivity/Wi-Fi/other) ▪ Completion of electronic PROM data (pre-CTx and mid-CTx assessments) by patients and successful transfer to study server ▪ Completion of electronic clinical and demographic patient data and successful transfer to the study server

	▪ Completion of electronic case note reviews and successful transfer to the study server. All clinical sites that meet the afore-mentioned requirements will proceed to Part 2 of the project. In those clinical sites where all or part of the afore-mentioned requirements are not met, every effort will be made for issues to be resolved during Part 1. Where however, despite all efforts to meet the afore-mentioned requirements, issues remain unresolved thus posing a risk to the project's conduct, clinical sites will be excluded. Excluded clinical sites will be replaced or, if this proves challenging or not feasible, recruitment of patients will be re-allocated to the remaining participating clinical sites. <u>Patient Demographic/Clinical Data (Parts 1 and 2)</u> A Patient Demographic Characteristics Pro-forma will be completed electronically by the research nurse/assistant/designated healthcare professional at the start of the study, including variables such as age, gender, marital status, number and age of children, educational attainment, income, ethnicity, lifestyle behaviours (i.e. diet, smoking, alcohol consumption, exercise) and current employment type/status. Patients will also be asked to state their preferred mode of data collection for follow-up data (i.e. post a maximum of 6 cycles of chemotherapy treatment). Research nurses/assistants/designated healthcare professionals will be reviewing the patients' medical records (following patient consent) to complete an electronic clinical characteristics pro-forma, including variables such as cancer diagnosis, stage of disease, cancer treatment plan, chemotherapy regimen, time since diagnosis, current medications and existing co-morbidities. Members of the clinical team will also be asked to assess the patient's performance status through use of the ECOG performance status scale. Case note reviews will also be conducted at the end of each cycle of chemotherapy as part of the cost-effectiveness evaluation. <u>ePROMs (Parts 1 and 2)</u> The outcome measures used in this study have been selected following a review of the literature as advocated by the MRC framework for complex interventions. These PROMs coincide with the study hypotheses and have been selected as the best available and most appropriate measures of the outcomes/endpoints identified in Section 6, thus providing evidence to substantiate their use within this project. Primary Outcome Measure: ▪ Memorial Symptom Assessment Scale (MSAS) Secondary Outcome Measures: ▪ Functional Assessment of Cancer Therapy-General (FACT-G) ▪ Supportive Care Needs Survey-Short Form 34 (SCNS-SF34) ▪ State-Trait Anxiety Inventory-Revised (STAI-Y) ▪ Communication and Attitudinal Self-Efficacy scale for cancer (CASE-Cancer)

	▪ Work Limitations Questionnaire (WLQ) ▪ EuroQol (EQ-5D) ▪ Client Services Receipt Inventory (CSRI) <u>Assessment of Changes in Clinical Practice (Parts 1 and 2)</u> In order to determine changes in clinical practice across the participating clinical sites and countries as a result of the implementation of the ASyMS intervention, a mixed-methods sequential explanatory design will be adopted. The complementary nature of this approach to data collection will ultimately permit understandings and contextualisation of changes in clinical practice by collecting data from professionals at baseline (Part 1) and from professionals and patients at the end of Part 2. <u>Economic Evaluation of ASyMS (Parts 1 and 2)</u> A cost-effectiveness analysis will be conducted from both a health/social care and a societal perspective. The costs of the intervention itself will be calculated by making use of data on ASyMS equipment distributed to patients and staff and patient training required for its use. Data on the cost-effectiveness of the ASyMS intervention will be collected via several sources including the EQ-5D, CSRI, case note reviews, and costing templates. Case note reviews will require access to medical records in order to determine relevant information such as cost due to change in medication, hospitalisation, GP/consultant visits, time spent on symptom management and other health resource use. <u>Development of predictive risk models (PRMs) (Part 2)</u> The PRMs will be developed in three distinct parts that will build on each other. 1. Development of the PRMs Using Existing Data The first stage of development will use existing data of the research team and data collected as part of the eSMART study to develop PRMs for use in patients with breast, colorectal and haematological cancers. Data will be analysed from previous studies (see Section 9). 2. Analysis of Prediction Capabilities The PRMs developed will be applied to the data collected from patients participating in the active chemotherapy part of the RCT (*n*=100 patients per cancer type, randomly selected from the total of those recruited) and statistically analysed to assess their prediction capabilities. The variables that will be identified as critical components of the PRMs will be extracted from the data set and sent for analysis. Outcomes to be assessed will include PRM ability to (a) predict an accurate trajectory of each symptom for a given individual; (b) identify symptom clusters; and (c) learn and adapt as new data about an individual is "learnt" as patients progress through their treatment.
Main Parameters of Safety	▪ In the interest of patient safety, patients who will be using the ASyMS intervention will be reminded that in cases where a failure in the technology occurs, standard care will apply throughout their participation in the study. ▪ In the interest of patient safety, clinicians will be reminded that in cases where a failure in the technology occurs, standard care

	will apply for patients in the intervention group throughout their participation in the study. ▪ In addition, all patients will receive contact details (in the patient information sheet) for use in the event of a problem with their participation in the study. ▪ Standard care will apply at all times for patients in Part 2 of the study who are randomly allocated to the control group.
Assessment Schedule	See Section 5.1 – Study flow chart
Data Analysis	Part 1. A combination of data analysis approaches involving data synthesis from systematic reviews and content analytic approaches to advisory group feedback (Preparatory work) and descriptive statistics and content analytic methods for feasibility testing data (Feasibility Testing Period). Part 2. A combination of data analysis approaches will be employed depending on the nature of the data (i.e. quantitative or qualitative). ▪ Repeated-measures analysis utilising mixed models ▪ Thematic analysis for interview/focus group data ▪ Cost-benefit analysis ▪ Latent variable analysis ▪ Descriptive and inferential statistics
Duration of Study Period (per patient)	Part 1 (Feasibility Testing). Estimated maximum duration of participation per patient: Approximately 2 months. Part 2. Estimated minimum duration of participation per patient: 12 weeks. Estimated maximum duration of participation per patient: Approximately 18 months.

5.1 STUDY FLOW CHART

Procedures	Part 1					Part 2																
		Feasibility Testing				Pre-trial period		Intervention Phase (up to 6 cycles)										Follow-up Phase (up to 12 months)					
	Preparatory period	Screening	Post-screening	Pre-CTxA	Pre-CTxB	Screening	Post-Screening	Baseline (Pre-CTx1)	Mid-CTx1	Pre-CTx2	Mid-CTx2	Pre-CTx3	Mid-CTx3	Pre-CTx4	Mid-Ctx4	::	Pre-CTxf	Mid-CTxf	Transition ePROMs	3 m post-CTxf*	6 m post-CTxf*	9 m post-CTxf*	12 m post-CTxf*	Post-trial period
1. Review of local and international guidelines for symptom assessment and management	×																						
2. Patient advisory group	×																						
3. Clinician advisory group	×																						
4. Translation and cultural adaptation of study components	×																						
5. Evaluation of the technological readiness of participating sites	×																						
6. Refinement of risk algorithms	×																						
7. Standardisation of responses to symptom alerts	×																						
8. Assessment of inclusion/exclusion criteria		×				×																	
9. Provide eligible patients with study information		×				×																	
10. Obtain written informed consent			×				×																
11. Patient randomisation and ID							×																
12. Random selection of patients for mid-CTx3 assessment							×																

Procedures	Part 1					Part 2																		
		Feasibility Testing				Pre-trial period		Intervention Phase (up to 6 cycles)											Follow-up Phase (up to 12 months)					
	Preparatory period	Screening	Post-screening	Pre-CTxA	Pre-CTxB	Screening	Post-Screening	Baseline (Pre-CTx1)	Mid-CTx1	Pre-CTx2	Mid-CTx2	Pre-CTx3	Mid-CTx3	Pre-CTx4	Mid-Ctx4	…	Pre-CTxf	Mid-CTxf	Transition ePROMs	3 m post-CTxf*	6 m post-CTxf*	9 m post-CTxf*	12 m post-CTxf*	Post-trial period
13. Collect patients clinical and demographic data			×				×																	
14. ECOG Performance status								×																
15. Collection of PROMs data:																								
▪ MSAS				×	×			×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
▪ FACT-G				×	×			×		×		×		×		×	×		×	×	×	×	×	
▪ SCNS-SF34				×	×			×		×		×		×		×	×		×	×	×	×	×	
▪ CASE-Cancer				×	×			×		×		×		×		×	×		×	×	×	×	×	
▪ STAI-Y				×	×			×		×		×		×		×	×		×	×	×	×	×	
▪ WLQ				×	×			×		×		×		×		×	×		×	×	×	×	×	
▪ EQ-5D				×	×			×		×		×		×		×	×		×	×	×	×	×	
▪ Adapted CSRI				×	×			×		×		×		×		×	×		×	×	×	×	×	
16. Case-note review				×	×			×		×		×		×		×	×		×					
17. Patient training to the use of the ASyMS technology				×				×[1]																
18. Clinician training to the use of the ASyMS technology				×		×																		
19. ASyMS intervention				Daily					Daily throughout chemotherapy treatment (up to a maximum of 6 cycles)[1]															
20. Assessment of Changes in Clinical Practice Questionnaire	×																							×

Procedures	Part 1					Part 2																	
		Feasibility Testing				Pre-trial period		Intervention Phase (up to 6 cycles)											Follow-up Phase (up to 12 months)					
	Preparatory period	Screening	Post-screening	Pre-CTxA	Pre-CTxB	Screening	Post-Screening	Baseline (Pre-CTx1)	Mid-CTx1	Pre-CTx2	Mid-CTx2	Pre-CTx3	Mid-CTx3	Pre-CTx4	Mid-Ctx4	…	Pre-CTxf	Mid-CTxf	Transition ePROMs	3 m post-CTxf*	6 m post-CTxf*	9 m post-CTxf*	12 m post-CTxf*	Post-trial period
21. Focus groups/interviews – patients (perceptions and PRMs)																			×					×
22. Focus groups/interviews – clinicians																								×
23. Development and testing of PRMs	×	×	×	×	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	

Abbreviations: MSAS – Memorial Symptom Assessment Scale; FACT-G – Functional Assessment of Cancer Therapy-General; SCNS-SF34 – Supportive Care Needs Survey-Short Form 34; STAI-Y – State-Trait Anxiety Inventory-Revised; CASE-Cancer – Communication and Attitudinal Self-Efficacy scale for cancer; WLQ – Work Limitations Questionnaire; EQ-5D – EuroQol; CSRI – Client Services Receipt Inventory; PRM – Predictive Risk Model; ASyMS – Advanced Symptom Management System; CTx – Chemotherapy cycle; TR – Clinical trial; FU – Follow-up; F – Feasibility period; f – Final cycle; ECOG – Eastern Cooperative Oncology Group; ID – Identification number; w – Week; m – Month.

*Follow-up assessments will be conducted through use of a mixed-mode data collection approach, whereby patients will be invited to choose between clinic visits, telephone calls or internet surveys in order to provide PROM data.

[1]Intervention group only.

6 SUMMARY OF STUDY DESIGN AND RATIONALE

6.1 Introduction

Over 3 million people are diagnosed with cancer each year in Europe [1] and cancer incidence worldwide is set to increase by at least 65% over the next 20 years [2]. Cancer is recognised as 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 [3].

Chemotherapy is a core treatment for cancer, and recent advances have resulted in considerable increases in overall cancer survival rates. Nevertheless, chemotherapy toxicity often leads to distressing and potentially life-threatening side-effects, which are associated with poor treatment adherence, impaired health-related quality of life (HR-QoL), infections and possibly an increase in treatment-related mortality [4]. Such toxicities not only occur during the acute part of treatment but can persist into survivorship. Symptoms that persist or manifest themselves after the end of treatment can increase the long-term burden on individuals [5] and create significant costs for the healthcare system.

Effective symptom assessment is therefore paramount for patients with cancer treated with chemotherapy. Yet, symptoms associated with chemotherapy are not always optimally assessed and managed, and the traditional retrospective methods of symptom assessment that persist in clinical practice often fail to identify patients' needs in a timely manner. Poor symptom assessment and management results in impairments in HR-QoL and physical and psychosocial well-being, exacerbated supportive care needs and increased time spent in hospital, which can adversely affect survivorship [5] and not only affect patients but also their families and carers [6]. Of note, demographic characteristics such as patient age and gender as well as socio-economic characteristics may be key moderators of symptom prevalence and severity, and psychosocial adjustment to cancer treatment.

Given the substantial increase in the number of people with cancer who will receive chemotherapy, an urgent need exists for more effective solutions to deliver supportive care to ensure optimal patient outcomes. This is compounded by the transition of cancer services, within Europe and beyond, from traditional in-patient care towards care delivered within local settings [7]. This shift of care delivery means that many patients are required to engage in self-care activities to prevent or reduce the severity of numerous and complex side effects [7] and make important health decisions when at home in the absence of clinicians [8]. Supporting a shift in clinical practice with innovative technological systems affords a solution to the increasing demands placed on acute care by enabling the delivery of care in the home and rural setting [9, 10]. Such remote monitoring systems facilitate the provision of clear lines of real-time communication between patients and their health care providers [9]. The evidence to support the use of remote patient monitoring is demonstrated by its effectiveness in improving health outcomes and cost savings as a result of decreased utilisation of health services [9].

To date, the most evolved remote monitoring system to monitor and manage the toxicities of cancer treatment is the Advanced Symptom Management System (ASyMS), which has been developed by a number of the collaborators in conjunction with cancer clinicians and people with cancer [11-20]. ASyMS is a mobile phone-based remote-monitoring system that enables the 'real-time' monitoring of patients' symptoms through use of a patient-reported outcome measure (PROM). The use of PROMs is advocated as an effective way to directly identify aspects of a patient's health status [21]; enhance management of treatment toxicities; alleviate patient anxiety; and promote self-care self-efficacy [22]. Combined with technology-driven interventions that are able to capture symptom data in real-time, electronic PROMs (ePROMs) allow rapid clinical decision-making and interventions to improve patient outcomes [23], and

enable the delivery of high quality care irrespective of distance in a variety of settings [10] and economic or cultural contexts.

By enabling real-time measurements of patients' symptoms, ASyMS facilitates immediate, tailored management of cancer treatment-related toxicities in the home care setting, and automatic and immediate triaging of care where patient symptoms exceed clinical norms as indicated in **Figure 1**.

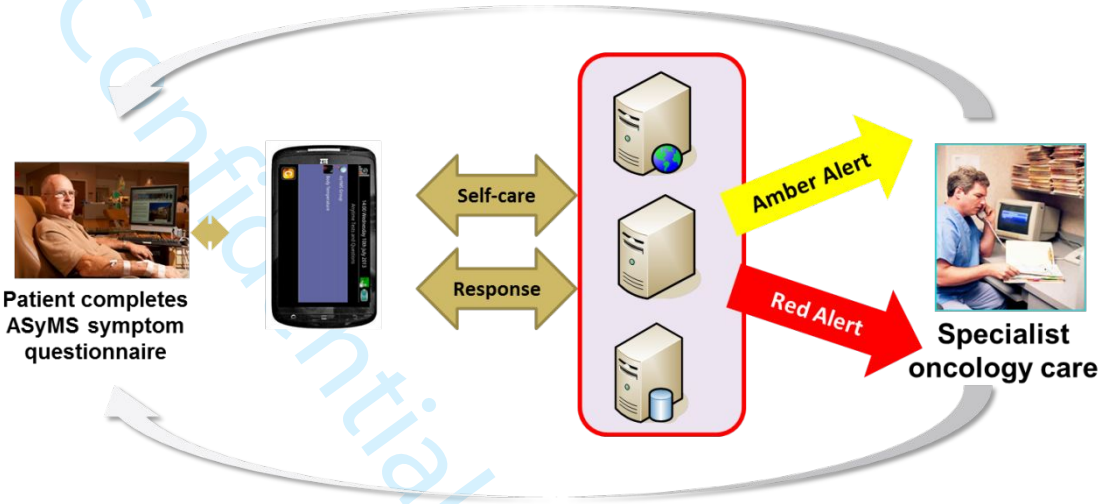

Figure 1. The ASyMS remote monitoring system.

Complementary to such technological innovations is the advent of Predictive Risk Models (PRMs) that enables 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 [24]. Collectively seen, the technologically driven real-time symptom monitoring and predictive risk modelling will allow for a timely, high quality, person-centred supportive care, whose durable effects can support and empower those living with and beyond cancer. Such advances will lead to increased levels of patient safety by assessing risks and mitigating these with optimal symptom management interventions.

The eSMART study will build upon the work to date and demonstrate the effects of the ASyMS intervention on key patient outcomes and delivery of care provided to people with cancer during and after chemotherapy. More specifically, utilising the ASyMS intervention, eSMART is expected to reduce the symptom burden experienced by patients receiving chemotherapy; improve patient HR-QoL and reduce anxiety and supportive care needs during acute treatment and at one-year post-intervention follow-up; increase self-efficacy; reduce chemotherapy toxicity-related work limitations; be cost-effective compared to standard care for the management of chemotherapy-related toxicity and result in changes in clinical practice and improved delivery of care for patients with cancer.

6.2 Summary of Study Design

The eSMART programme of work comprises two parts of work that will take place over a period of five years.

The current study will be informed by the Medical Research Council Complex Interventions Framework [25-27]. E-health technological interventions are regarded as 'complex' because they are built up from a number of components that involve theoretical understanding of how the use of technology benefits patients, and require the involvement of multiple agencies. The MRC Framework proposes a cyclical, multi-method process in the evaluation of these components that takes place in partnership with the target population[28]. In addition, the Holistic Framework to improve the Uptake and Impact of e-Health Technologies developed by van Gemert-Pijnen et al. [29] will be used to inform the current study. According to this framework, six fundamental working principles underpin the development of e-health technologies (**Table 1**). The framework provides comprehensive development strategies that can be used in a forward (development) and backward (summative evaluation) process, but is also flexible to accommodate for time, policy and financial challenges in clinical practice [29].

Table 1. Working principles of the Holistic Framework for the Uptake and Impact of e-Health Technologies [29]

Principle	Concept
1. e-Health Technology Development is a Participatory Process	"Stakeholder participation is essential. Stakeholders' involvement spans the full development process, starting from contextual inquiry and ending with summative evaluation."
2. e-Health Technology Development Involves Continuous Evaluation Cycles	"Development is an iterative, flexible, and dynamic process resulting in concepts of the technology (from ideation to prototypes). […] Evaluation as such is a cyclic, longitudinal research activity interwoven with all stages in the development process and as such without a fixed end (formative and summative evaluation)."
3. e-Health Technology Development is Intertwined With Implementation	"…the conditions for implementation must be taken into account right from the start (contextual inquiry and value specification)."
4. e-Health Technology Development Changes the Organization of Health Care	"The development of e-Health technology in itself can be considered as the creation of new processes and infrastructures for health care delivery. It may reshape health care since it intervenes with traditional care characteristics such as the division of labor, or time- and place-dependant deliver."
5. e-Health Technology Development Should Involve Persuasive Design Techniques	"[Patients] expect self-care technology to show understanding, to persuade them to do the right thing, or to provide rewards and appraisal for appropriate behavior. […] Particularly in the context of long-term care, it is important to develop technologies that can create bonding relationships with the end users. […] Via persuasive techniques, e-Health technologies can be designed to match user profiles, and to motivate or inspire patients to engage in self-management."
6. e-Health Technology Development Needs Advanced Methods to Assess Impact	"…need to understand *what* differences e-Health technologies can make in health care, *why* e-Health technologies make these differences, and *why* e-Health technologies may not have the expected impact. […] The challenge lies in the integration of data collection from multiple sources, using a mixed-methods research design."

6.2.1 Part 1: Preparation of the ASyMS technology for use in a European setting

Part 1 will entail:

- Patient and clinician advisory groups will be convened within each participating country to inform the conduct of the eSMART study. Representation will include people with breast cancer, colorectal cancer, Hodgkin's disease or non-Hodgkin lymphoma. Clinical groups will consist of specialist nurses, breast and colorectal oncologists, haematologists, pharmacists and allied health professionals all of whom provide supportive care.
- Review of local guidelines and resources for the assessment and management of chemotherapy related toxicity to ensure that ASyMS reflects local practice.
- Refinement of the ASyMS risk algorithms for symptom alerts.
- Standardisation of responses to symptom alerts across the participating sites.
- Translation of all study components into the required languages for use at the participating sites.

- Evaluation of the technological readiness of the participating sites for the deployment of ASyMS prior to Part 2.
- Feasibility testing of the ASyMS technology in each participating site (which will include testing of the electronic PROMS system, such as optimal time breaks). Up to 6 patients per site, i.e. *n*=2 per cancer type depending on the different cancer types being evaluated at each site (max. n=6 per participating site) will use the ASyMS technology over one cycle of chemotherapy (CTx) to evaluate each site in terms of the support/infrastructure required and ensure that the ASyMS technology is ready for full deployment in Part 2.
- Baseline data collection activities to form part of the Assessment of Changes in Clinical Practice and cost-effectiveness evaluation.

6.2.2 Part 2: Randomised controlled trial (RCT) to test the ASyMS intervention

Part 2 will aim to (1) test the effect of the ASyMS intervention on patient-reported outcomes during the first 6 cycles of active chemotherapy treatment and a year thereafter; (2) determine changes in clinical practice as a result of the application of the ASyMS intervention; (3) evaluate the cost-effectiveness of the ASyMS intervention, and (4) develop and evaluate PRMs to enhance the management of chemotherapy toxicity.

Part 2 will entail:

- ***Two-year RCT evaluating the effects of the ASyMS technology on patient-reported outcomes:*** A total of 1,108 patients with breast cancer, colorectal cancer, Hodgkin's disease (HD) or non-Hodgkin lymphoma (NHL) receiving at least 3 CTx of chemotherapy for the first time will be recruited to the RCT from a number of countries in Europe (Austria, Greece, Republic of Ireland, Norway, United Kingdom) over a period of two years. Patients will be randomly allocated to either the ASyMS technology (intervention group) or to standard care currently available at each site (control group). Patients allocated to the intervention group will use the ASyMS technology for a maximum of 6 cycles of chemotherapy. After a maximum of 6 cycles of chemotherapy both groups will be followed-up for a maximum of one year. Irrespective of study condition, patients will be asked to complete a clinical and demographic questionnaire at the start of the study, as well as a set of validated questionnaires at baseline, at each chemotherapy cycle (for a maximum of 6 cycles of chemotherapy), and at 3 monthly intervals up to a maximum of 12 months). Patient outcomes to be assessed will include symptom burden (primary outcome), quality of life, supportive care needs, self-efficacy, anxiety, health services access and costs and work limitations (secondary outcomes). In addition, mid-CTx assessments of the primary outcome (i.e. symptom burden) will take place during each cycle of chemotherapy (over a maximum of 6 cycles) for a randomly selected (during initial randomisation) subsample (30% of the total of recruited patients) in order to capture additional data on symptom burden at this time.

- ***Assessment of changes in clinical practice:*** To determine changes in clinical practice across the participating clinical sites, a mixed-methods sequential explanatory design will be adopted. To help explain and contextualise changes in clinical practice, baseline data will be collected during Part 1 and again at the end of Part 2. Assessment of Changes in Clinical Practice Questionnaires will be distributed via an online survey tool to professionals (data auditors and key clinicians) at each participating clinical site in each country in Part 1 to gather detailed information on current clinical processes and pathways, prior to the introduction of the ASyMS intervention. Data from the baseline questionnaires will be pooled for each site in each country to populate a detailed understanding of the current processes involved in the management of chemotherapy related toxicity, both during and out with working hours for each diagnostic group, as appropriate. A follow-up Assessment of Changes in Clinical Practice Questionnaire will then be distributed via an online survey tool to data auditors and key clinicians at each participating clinical site in each country to gather detailed information on clinical processes and pathways, post-introduction and use of the ASyMS intervention. Telephone/face-to-face interviews/focus groups will also be undertaken with a range of

professionals upon collection of quantitative data at the end of Part 2. Patient perceptions will also be explored - a small number of patients (5-10 from each clinical area) who receive the mobile phone will be invited to participate in a telephone/face-to-face interview or focus group at or near the end of their participation in the Intervention Phase. This will explore their perceptions of care and the use of technology.

- ***Cost-effectiveness evaluation:*** Data on the cost-effectiveness of the ASyMS intervention will be collected via several sources including a patient-reported health measure (i.e. EQ-5D), patient cost questionnaires (CSRI), case note reviews, and costing templates. Information collected will include the following: visits to accident and emergency; out-patient/day care appointments; private healthcare costs; medications (prescription and non-prescription drugs) and medical equipment; time taken off work to attend health/social care appointments; time/costs to travel for health/social care appointments/other related costs.

Development and evaluation of PRMs: The development of PRMs will be achieved in tandem with the on-going RCT. The PRMs developed will combine clinical, demographic, social, and health service data collected from previous studies, as well as the current study, to inform the predictions made. Two face-to-face/telephone interviews/focus groups with patients (in their native language) (n=1) and clinicians (n=1) (who can speak English sufficiently well enough to actively participate) will be conducted in each country to explore their perceptions of the utility of the PRMs in clinical practice.

6.3 Potential Risks and Benefits

6.3.1 Patients

No physical risks are anticipated due to the non-invasive nature of the intervention. However, people affected by cancer constitute potentially vulnerable populations; hence, considerable care will be taken to avoid causing any distress to them during the study. First, it is recognised that the daily completion of the ASyMS technology symptom questionnaire and/or the collection ePROM data can encourage patients to focus more on their experiences than if they had not been asked to complete them. Some participants could find this experience distressing. A patient support flyer (e.g. Macmillan Cancer Support in the UK or similar/equivalent in each country) with contact information will be given to all participants at the time of recruitment should anyone feel the need to receive additional support at this or later points during the study. Patients will also be reminded to speak with their GP/oncology consultant/family physician, who will have previously been formally informed (with the patient's consent) of the patient's participation in the study. It will also be the responsibility of the research nurse/assistant/designated health professional, who will follow each patient at each CTx, to ensure that participation in the study does not cause any adverse effects for patients. The research assistant/research nurse/designated health professional will talk through any issues with patients as and when they arise. If patients become overly distressed, the research nurse/assistant/designated health professional will notify a member of the clinical team, who will then contact the patient to offer support. In cases where no resolution is achieved, the research nurse/assistant/designated health professional will advise the patient to exit the study if they so wish, without this having any effect on the standard of care and treatment they receive.

Second, some patients may feel uncomfortable in using the mobile phone technology to report their symptoms. However, the patients will receive training at the start of the study and will not be asked to participate in the study until they feel comfortable in using the mobile phone and are able to successfully send symptom information. Furthermore, patients will be advised

that they have 24-hour contact with staff at the clinical site, should they experience any problems in relation to the technology. Should the mobile phone be lost or damaged, patients will be issued with a replacement handset by the research assistant/research nurse/designated health professional at the hospital site as soon as possible. Damaged handsets will be returned to the research team for investigation. Patients will be reassured that a lost or damaged handset will not impact their participation in the study. Staff at the participating clinical sites will have 24-hour technical support manned by the software developer company that they can use if they experience any technical problems with the ASyMS technology. In addition to patient contact details being stored on the ASyMS website for access when alert handling is required, a hard copy of the patient's study ID number, name and contact details will be kept locked away at the participating site in case the ASyMS server malfunctions or is unavailable. Thus, the clinician (i.e. alert handler) will still be able to contact the patient to assess their symptoms and intervene.

Finally, patients may perceive participation in telephone/face-to-face interviews/focus groups as an inconvenience as they may have to spend some extra time in the hospital in order to take part in the interviews. The research team, study partners and local site principal investigators (PIs) will endeavour to arrange the focus groups at a time that is most convenient for all participants and will ensure that the maximum duration of the telephone/face-to-face interviews/focus groups is one hour. If patients become overly distressed during the interview, the research nurse/assistant will notify a member of the clinical team, who will then contact the patient to offer support. In cases where no resolution is achieved, the research nurse/assistant will advise the patient to leave the interview/focus group, without this having any effect on the standard of care and treatment they receive.

The anticipated improvement in symptom assessment and timely symptom management suggests that patients in the intervention group are expected to be directly benefited by their participation in this RCT. Although they may not be directly benefited from taking part in this study, even patients in the control group may find their participation beneficial in an indirect manner. Through completing the data collection ePROMs, participants will have the opportunity to reflect on their experience, which might urge them to discuss their feelings with members of the clinical team, and thus seek and receive more help.

6.3.2 Professionals

Professionals may perceive completion of questionnaires and/or participation in telephone/face-to-face interviews/focus groups as an inconvenience as they may have to take some time out of their working day to take part in these activities. The research team will endeavour to arrange the telephone/face-to-face interviews/focus groups at a time that is most convenient for all participants and will ensure that the maximum duration of the telephone/face-to-face interviews/focus groups is one hour. In addition, all telephone/face-to-face interviews/focus groups will take place at the clinical sites during working hours for convenience.

The benefits of participating in the study for professionals are that they will be able to contribute as professionals their perspectives of the ASyMS intervention. It is hoped that this will ensure that the ASyMS intervention meets the needs of both patients and professionals using the system as part of their care.

6.3.3 Researchers

In general, no major risks are anticipated for the researchers themselves as the entire study will be undertaken at already identified clinical sites, access to which is facilitated by local site PIs. However, it is acknowledged that members of the research team who will be conducting consecutive telephone/face-to-face interviews/focus group interviews with patients with cancer might be exposed to patients' experiences of illness and treatment during these interactions. Emotional support will be in place for all members of the research team should they feel the

need to seek it at all times during the study. A number of strategies will be employed to prevent emotional distress of researchers, including debriefing in groups or with peers as a source of support, support from line managers, and use of a reflective diary to manage emotional distress. In addition, members of the research team will have access to free and confidential support and counselling services at the University of Strathclyde.

6.4 Study Rationale

The primary aim of eSMART is to evaluate the short and long term impact of the ASyMS technology on patient reported outcomes in people with breast cancer, colorectal cancer or haematological malignancies (i.e. HD or NHL) receiving chemotherapy for the first time. In addition, eSMART will evaluate the cost-benefit of remote patient-monitoring and changes in clinical practice as a result of the application of the ASyMS intervention in different European healthcare settings. Utilising data from this study, eSMART will conclude with the development of PRMs to predict chemotherapy related toxicity for people with breast, colorectal and haematological cancers receiving chemotherapy.

The model of care proposed through the eSMART programme of work (**Figure 2**) has been developed from patient experience in collaboration with the European Cancer Patient Coalition (ECPC). Utilising a combination of real-time symptom assessment, PRMs and clinical algorithms, this model of care will facilitate the early identification of chemotherapy related toxicities, early within their trajectory, as and when they occur. This anticipatory model of care supports symptom management within the patient's home, where the early toxicities of chemotherapy can be managed, utilising self-care and local community services. When required, this model of care also facilitates rapid re-entry into acute care services for those patients experiencing more complex or life threatening toxicities, providing quick access to specialist staff in the patient's own hospital, and the initiation of appropriate interventions.

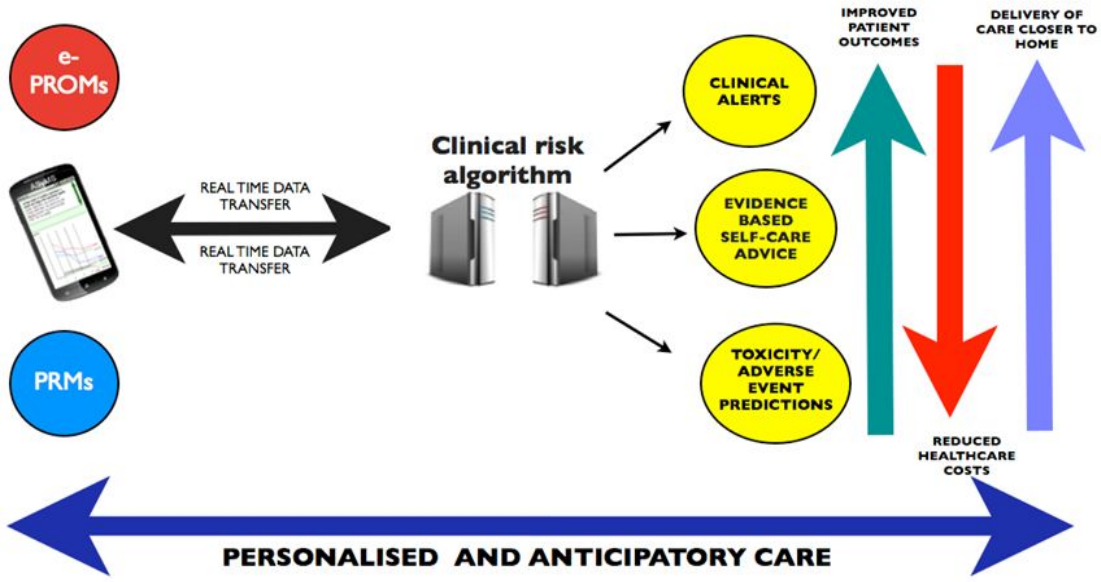

Figure 2. The eSMART model of care.

6.4.1 Rationale for Study Design

High quality RCTs are placed at the top of level-of-evidence classifications in evidence-based research [30]. In these classification systems, significant results of an RCT are considered to be more authoritative than any other type of clinical research information.

In agreement with this classification scheme, a repeated measures, parallel group, stratified randomised controlled trial (RCT), will be conducted to demonstrate the effects of the ASyMS intervention in supporting patients who receive chemotherapy treatment through individualised symptom management [31].

Part 1 will include preparatory work to refine the ASyMS intervention for use in a multi-national context, and conclude with a feasibility testing period that will establish the technological readiness of the system prior to use in the main trial (i.e. Part 2).

Part 2 will test the short- (i.e. during the Intervention Phase) and long-term effects (i.e. up to one year following a maximum of 6 cycles of chemotherapy) of the ASyMS intervention versus standard care through a repeated-measures, parallel-group stratified RCT across the participating countries. The longitudinal nature of the trial will aid at establishing sustainability of intervention effects and further stress its benefits when compared to standard care.

Importantly, in order to be able to document applicability of the trial's results in clinical practice and ensure that the needs of end-users are fully met, economic evaluation, quantitative and qualitative data analyses will also be performed in Parts 1 and 2 in accordance with latest recommendations for pragmatic research in healthcare [32, 33].

6.4.2 Rationale for Study Endpoints

6.4.2.1 Part 1: Preparatory Work and Feasibility Testing period

Achievement of the designated endpoints will ensure that the ASyMS technology is up-to-date with current European and international guidelines for symptom management, it is translated and culturally adapted to partner countries, and reflects/associates with current clinical practice at the participating sites. Standardisation of responses to symptom alerts will enhance the methodological robustness of the proposed RCT (Part 2), thus reducing interference of bias related to individual clinician responses that may blur the actual intervention effects. In addition, preparation of the clinical sites to host the ASyMS intervention will be evaluated during the feasibility testing period to ensure that the RCT is conducted in a seamless manner.

6.4.2.2 Part 2: RCT

6.4.2.2.1 Primary Endpoint

As previously stated, effective symptom assessment and management during chemotherapy is paramount to prevent impairments in HR-QoL, physical and psychosocial well-being, exacerbated supportive care needs and increased time spent in hospital [5]. One key aspect is that symptom assessment and management is performed on the basis of adequate symptom information that is made available to clinicians in a timely manner. A recent systematic review of clinical trials evaluating the effectiveness of the routine collection of patient feedback to improve patient outcomes, processes of care, and health service outcomes in cancer care identified physical symptoms as an area amenable to the effects of such practices [34]. In agreement with the target goals of the ASyMS intervention, reduction in symptom burden during active chemotherapy was selected as the primary endpoint of this RCT. It is anticipated that, compared to the control group, patients in the intervention group will have reduced symptom burden (i.e. significantly lower total MSAS scores) during chemotherapy (maximum 6 cycles).

6.4.2.2.2 Secondary Endpoints

In agreement with the target goals of the ASyMS intervention, reduction in symptom burden up to one-year following a maximum of 6 cycles of chemotherapy was selected as a secondary endpoint of this RCT. It is anticipated that, compared to the control group, patients in the intervention group will have reduced symptom burden (i.e. significantly lower total MSAS scores) in the long-term during follow-up assessments. In addition, by targeting symptom assessment and management, a number of additional positive outcomes are anticipated relating to HR-QoL (i.e. significant improvement in total FACT-G scores), supportive care needs (i.e. significant improvement in total SCNS-SF34 scores), patient self-efficacy (i.e. significant improvement in total CASE-Cancer scores), anxiety (i.e. significant improvement in total STAI-Y scores), return to work (i.e. significant improvement in total WLQ scores), health services access and costs (i.e. cost effective compared to standard care as illustrated via the EQ-5D, CSRI and case note reviews) and processes of care (i.e. significant changes in clinical practice) as a result of the use of the ASyMS intervention compared to standard care. Outcomes in these areas have been selected as important secondary endpoints. Whilst some tentative positive evidence exists with regard to improvement in HR-QoL, reduction in supportive care needs, and enhancement of patient-clinician communication [34], this RCT will aim to add to the current knowledge base substantial evidence with regard to these areas and further explore the potential of the intervention to boost patient self-management skills, and accelerate patient rehabilitation and return to normal. Additional endpoints will include the investigation of positive effects on current clinical practice and care processes, which complemented by favourable cost-effectiveness outcomes will help support our arguments for the employment of this and similar interventions in clinical practice in the future. Despite recognition of the importance of such information to establish a new paradigm in modern cancer care, evidence is still lacking and urgently needed [34]; this RCT is anticipated to contribute greatly to this end.

6.4.2.2.3 Exploratory Endpoint

Predictive Risk Models (PRMs) are statistical prediction tools developed to provide quantitative estimates of the probability of a specific event for a specific patient [24]. PRMs have the ability to provide patients and clinicians with personalised predictions of the risk of experiencing chemotherapy-related toxicities, thus facilitating the delivery of tailored preventative interventions. It is widely accepted that applying risk modelling techniques to clinical data has enormous potential to improve the quality of patient care and increase the survival rate of patients [35]. Risk modelling can provide a means for early recognition of serious, often life-threatening events such as sepsis when early detection and treatment can result in significantly lower mortality rates [36]. Within cancer care, there is limited use of risk modelling to predict chemotherapy-related toxicities [37, 38]. Bodies of work focus on predictors of survival and life threatening toxicities such a febrile neutropenia [39, 40]. Early work conducted by members of this research group developed ASyMS-SERAT (Side-Effect Risk Modelling Tool), which incorporated risk models to assess the likelihood of an individual experiencing chemotherapy related toxicities [41]. eSMART will build on this to further develop PRMs for patients with breast, colorectal and haematological cancer.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Study Objectives

7.1.1 Part 1: Aims

The aims of Part 1 will be to undertake refinement of the risks algorithms used as part of the ASyMS technology; prepare the participating clinical sites for full deployment of the ASyMS technology in Part 2; and ensure that translated and culturally adapted versions of the ASyMS technology, data collection PROMs and additional supporting documentation are in place before Part 2 begins. Part 1 will conclude with a feasibility testing period, during which the ASyMS technology will be tested at its participating site for its technological readiness for a wide-scale application during Part 2 of this study.

Therefore, the objectives of Part 1 will be the following:

7.1.1.1 Preparatory work

- Review the literature and international/national/local guidelines for the assessment and management of chemotherapy-related toxicity to ensure that ASyMS reflects local and current practice.
- Refine both the risk algorithms for symptom alerts used as part of the ASyMS technology and the system content (e.g. self-care library) based on a review of international guidelines and local practice, and patient and clinician feedback.
- Standardise responses to symptom alerts across European sites.
- Prepare the participating clinical sites for the application of ASyMS through assessment of infrastructure and human and material resource requirements.
- Translate and culturally adapt ASyMS, the data collection PROMs and additional supporting documentation into the required languages for use at the participating sites.

7.1.1.2 Feasibility testing

- Feasibility testing and assessment of the technological readiness of the ASyMS system at the participating sites in preparation for Part 2.

7.1.2 Part 2: Aims

The primary aim of Part 2 will be to evaluate the short- and long-term impact of the ASyMS technology on patient-reported outcomes in people with breast or colorectal cancer or haematological cancers, specifically HD or NHL, receiving chemotherapy treatment for the first time. In addition, eSMART will evaluate the cost-effectiveness of the ASyMS technology, as well as changes in clinical practice that may follow its full deployment at the different European healthcare settings. Utilising eSMART data, PRMs will also be developed and tested regarding their accuracy in predicting chemotherapy-related toxicity in patients with breast, colorectal or haematological cancers receiving chemotherapy.

The objectives of Part 2 are detailed below.

7.1.2.1 Primary Objective

To show whether, compared to standard care, the ASyMS intervention can lead to reduced symptom burden during active chemotherapy for breast cancer or colorectal cancer or HD or NHL as evidenced by statistically significantly lower total MSAS scores (i.e. primary outcome) during chemotherapy (maximum 6 cycles).

7.1.2.2 Secondary Objectives

To show whether, compared to standard care, the ASyMS intervention can lead to:

- Reduction in patient symptom burden (total MSAS score) up to one-year post-intervention (maximum 6 cycles) follow-up, compared to standard care, as evidenced by statistically significantly lower total MSAS scores at pre-specified time-points and at the end of the one-year period (total sample, subgroups according to type of diagnosis, subgroups according to country).
- Reduction in symptom burden (total MSAS score) at mid-CTx (i.e. peak symptom burden), compared to standard care, as evidenced by statistically significantly lower total MSAS scores.
- Increase in patient overall HR-QoL and HR-QoL domain scores (FACT-G scores) during active chemotherapy (for a maximum of 6 cycles) and up to one-year follow-up thereafter (total sample, subgroups according to type of diagnosis, subgroups according to country).
- Reduction in patient overall supportive care needs and domains of need during active chemotherapy (maximum 6 cycles) and up to one-year follow-up thereafter (SCNS-SF34 total and subscale scores) compared to standard care adjusting for baseline scores (total sample, subgroups according to type of diagnosis, subgroups according to country).
- Reduction in levels of anxiety during active chemotherapy (for a maximum of 6 cycles) and up to one-year follow-up thereafter (STAI-Y state and/or trait subscales) compared to standard care adjusting for baseline scores (total sample, subgroups according to type of diagnosis, subgroups according to country).
- Improvement in patient self-efficacy (total CASE-Cancer scores) during active chemotherapy (for a maximum of 6 cycles) and up to one-year follow-up thereafter compared to standard care adjusting for baseline scores (total sample, subgroups according to type of diagnosis, subgroups according to country).
- Fewer work limitations (total WLQ scores) during active chemotherapy (for a maximum of 6 cycles) and up to one-year follow-up thereafter compared to standard care adjusting for baseline scores (total sample, subgroups according to type of diagnosis, subgroups according to country).
- Health system costs of the ASyMS intervention (total sample and country-specific).
- Superior cost-effectiveness in terms of cost per QALY gained.
- Positive changes in clinical practice as a result of the ASyMS intervention (site/country-specific).

In addition, the following aspects will be investigated and assessed:

- The cost-effectiveness of the ASyMS intervention for the management of chemotherapy-related toxicity by combining resource use data with quality-adjusted life years (QALYs) measured with the EQ-5D and use of the CSRI.
- Changes in clinical practice as a result of the ASyMS intervention by promoting an anticipatory and preventative model of care that enables more care to be delivered in local settings.

7.1.2.3 Exploratory Objective

To develop and test PRMs to predict chemotherapy-related toxicity in patients with breast cancer, colorectal cancer, or haematological cancers (i.e. HD or NHL) by combining clinical, demographic, social, and health service data collected from previous studies, as well as the current study, to inform the predictions made. This component will move beyond traditional approaches to manage symptoms in patients receiving cancer chemotherapy to more tailored and anticipatory approaches.

7.2 Study Endpoints

7.2.1 Part 1

- Literature and international/national/local guidelines for the assessment and management of chemotherapy-related toxicity systematically and fully reviewed.
- Risk algorithms for symptom alerts refined based on review of guidelines and local practice, and patient and clinician feedback.
- Response to symptom alerts standardised across European sites.
- Participating clinical sites prepared in terms of infrastructure and human and material resource requirements.
- Assessment questionnaires translated and linguistically validated (where appropriate) into the required languages.
- Successful feasibility testing of the ASyMS technology at the participating sites through evaluation of a number of parameters to demonstrate the technological readiness of the system, with any issues tackled prior to full deployment in Part 2:
  - Training of patients/staff to use ASyMS
  - Registration of patients and clinicians on ASyMS
  - Use of patient handset (completion of symptom questionnaire, access to self-care, access to symptom graphs, library, useful contacts)
  - Transfer of data from patient handset to study server
  - Clinician access and log onto the ASyMS web portal
  - Ability of clinicians to deal with an alert using the ASyMS web portal
  - Ability of clinicians to log on and use ASyMS nurse handset for the receipt of alerts
  - Technological connectivity of ASyMS (mobile connectivity/Wi-Fi/other)
  - Completion of ePROM data by patients (pre-CTx and mid-CTx assessments) and successful transfer to study server
  - Completion of electronic clinical and demographic patient data and successful transfer to the study server
  - Completion of electronic case note reviews and successful transfer to the study server.

7.2.2 Part 2

7.2.2.1 Primary Endpoint

- Reduction in patient symptom burden (total MSAS score) during chemotherapy (up to a maximum of 6 cycles of chemotherapy), compared to standard care, as evidenced by statistically significantly lower total MSAS scores (primary outcome) over all cycles (maximum 6) after adjusting for baseline scores (total sample, subgroups according to type of diagnosis, subgroups according to country).

7.2.2.2 Secondary Endpoints

- Reduction in patient symptom burden (total MSAS score) up to one-year post-intervention (maximum 6 cycles) follow-up, compared to standard care, as evidenced by statistically significantly lower total MSAS scores at pre-specified time-points and up to the end of the one-year period (total sample, subgroups according to type of diagnosis, subgroups according to country).
- Reduction in symptom burden (total MSAS score) at mid-CTx (i.e. peak symptom burden), compared to standard care, as evidenced by statistically significantly lower total MSAS scores.
- Increase in patient overall HR-QoL and HR-QoL domain scores (FACT-G scores) during active chemotherapy (for a maximum of 6 cycles) and up to one-year follow-up thereafter (total sample, subgroups according to type of diagnosis, subgroups according to country).

- Reduction in patient overall supportive care needs and domains of need during active chemotherapy (maximum 6 cycles) and up to one-year follow-up thereafter (SCNS-SF34 total and subscale scores) compared to standard care adjusting for baseline scores (total sample, subgroups according to type of diagnosis, subgroups according to country).
- Reduction in levels of anxiety during active chemotherapy (for a maximum of 6 cycles) and up to one-year follow-up thereafter (STAI-Y state and/or trait subscales) compared to standard care adjusting for baseline scores (total sample, subgroups according to type of diagnosis, subgroups according to country).
- Improvement in patient self-efficacy (total CASE-Cancer scores) during active chemotherapy (for a maximum of 6 cycles) and up to one-year follow-up thereafter compared to standard care adjusting for baseline scores (total sample, subgroups according to type of diagnosis, subgroups according to country).
- Fewer work limitations (total WLQ scores) during active chemotherapy (for a maximum of 6 cycles) and up to one-year follow-up thereafter compared to standard care adjusting for baseline scores (total sample, subgroups according to type of diagnosis, subgroups according to country).
- Health system costs of the ASyMS intervention (total sample and country-specific).
- Superior cost-effectiveness in terms of cost per QALY gained.
- Positive changes in clinical practice as a result of the ASyMS intervention (site/country-specific).

7.2.3 Exploratory Endpoint

- Successful development and testing of PRMs for the prediction of study outcomes in patients with breast, colorectal or haematological cancers. Attempts will be made to develop and test PRMs that are unique to each type of cancer, as well as generic to oncology patients who are receiving chemotherapy.

8 PATIENT SELECTION AND WITHDRAWAL CRITERIA

Participant selection and withdrawal criteria will apply to potential participants in both Part 1 and Part 2. However, two separate groups of patients will be recruited for these separate Parts, following two separate screening and selection procedures. Part 1 patients will not be required to also participate in Part 2, and this will be explicitly stated during consent. A range of professionals will also be recruited to Parts 1 and 2 of the study.

8.1 Setting and Recruiting Sites (Parts 1 and 2)

Patients diagnosed with breast cancer, colorectal cancer, HD or NHL scheduled to commence chemotherapy for the first time (Part 1 and Part 2) or already receiving chemotherapy (Part 1 only) in the participating clinical sites will be screened for eligibility and invited to take part in the study.

Patients will be recruited to Parts 1 or 2 from a number of European countries/study partners (i.e. Austria, Greece, Republic of Ireland, Norway, and United Kingdom) over a period of 24 months (**Table 1**).

8.2 Population base (Parts 1 and 2)

Patients with breast cancer, colorectal cancer, HD or NHL receiving (Part 1 only) or scheduled to commence (Part 1 and Part 2) chemotherapy for the first time will be recruited to this study. These cancer types were selected for two reasons. First, chemotherapy is a core component of the treatment of these types of cancer. Second, the ASyMS intervention was developed for use in these patient populations and is ready for trialling within a European setting.

A range of Professionals involved in the delivery of care or data monitoring of people with breast cancer, colorectal cancer or haematological malignancies from each site in each country will also be recruited to Parts 1 and 2 of the study.

8.3 Inclusion criteria (Parts 1 – Feasibility Testing and 2 – RCT: Intervention Phase)

Patient Sample

Patients will be recruited to Part 1 (Feasibility Testing) according to the following inclusion criteria:

- Adults (≥18 years).
- Diagnosed with breast cancer, colorectal cancer, or a haematological malignancy (i.e. Hodgkins Disease or Non-Hodgkins Lymphoma).
- Scheduled to start chemotherapy treatment for the first time, or (if previous chemotherapy has been received), scheduled to receive chemotherapy for the first time in the last 5 years (however patients who have received chemoradiation for colorectal cancer **are** eligible for inclusion).
- Scheduled to receive a 2-, 3- or 4-weekly chemotherapy treatment, i.e. chemotherapy administered in repeated cycles of 14, 21 or 28 days, respectively.
- Scheduled to receive a minimum of 3 cycles of chemotherapy treatment.
- Physically/psychologically fit to participate in the study as confirmed by a member of the patient's multidisciplinary care team.
- Able to read, understand and write in the respective language.

Patients will be recruited to Part 2 (RCT: Intervention Phase) according to the following inclusion criteria:

- Adults (≥18 years).
- Diagnosed with breast cancer, colorectal cancer, or a haematological malignancy (i.e. Hodgkins Disease or Non-Hodgkins Lymphoma).
- Scheduled to start chemotherapy treatment for the first time, or (if previous chemotherapy has been received), scheduled to receive chemotherapy for the first time in the last 5 years (however patients who have received chemoradiation for colorectal cancer **are** eligible for inclusion).
- Scheduled to receive a 2-, 3- or 4-weekly chemotherapy treatment, i.e. chemotherapy administered in repeated cycles of 14, 21 or 28 days, respectively.
- Scheduled to receive a minimum of 3 cycles of chemotherapy treatment.
- Physically/psychologically fit to participate in the study as confirmed by a member of the patient's multidisciplinary care team.
- Able to read, understand and write in the respective language.

Professional Sample

Professionals will be recruited to Parts 1 and 2 of the study:

- Adults (≥18 years).
- Involved in the delivery of care or data monitoring of people with breast cancer, colorectal cancer, or haematological malignancies (i.e. HD or NHL).
- Able to provide informed consent.

8.4 Exclusion criteria (Parts 1 - Feasibility Testing and 2 - RCT)

Patients will **not** be considered for participation in either Part 1 (Feasibility Testing) or Part 2 (RCT: Intervention Phase) on the basis of the following exclusion criteria (patients will be automatically included in the follow-up phase unless they withdraw):

- Patients with breast cancer or colorectal cancer with a distant metastasis, i.e. stage IV disease as defined by the TNM/UICC (at the start of their chemotherapy treatment).
- Patients with a haematological malignancy (HD or NHL), who have B symptoms (at the start of their chemotherapy treatment).
- Scheduled to receive concurrent radiotherapy at any point over the planned course of chemotherapy treatment.
- Scheduled to receive weekly chemotherapy treatment.
- Diagnosed with the same type of cancer (i.e. where relapse has occurred) AND/OR another type of cancer (the only exception non-melanoma skin cancer) within the 5 years prior to recruitment to the study.
- Received chemotherapy treatment for any medical reason within the last 5 years (unless this is chemoradiation for colorectal cancer).
- Unable to provide written informed consent.

8.5 Refusal to Participate (Parts 1 and 2)

All eligible patients will be offered to take part in either Part 1 or 2. Any patient will be free to refuse participation. Although all patients will be asked for reason(s) for refusal, it will not be mandatory for patients to provide this information. However, capturing such information is useful for reporting purposes in terms of demonstrating the acceptability of the RCT. Reasons

for refusal will be recorded by the research nurse/assistant/designated health professional for those patients who choose to provide one.

No identifiable data will be recorded for patients who refuse to participate. However, non-identifiable data, including age (but not date of birth), gender, origin (i.e. clinical site and country), and type of cancer, will only be recorded in order for a comparison between consenting and non-consenting patients to be performed to further explore acceptability of the RCT.

8.6 Discontinuation and Withdrawal of subjects from the study (Parts 1 and 2)

For the purposes of the eSMART study the following definitions will be used:

Withdrawal - relates to any patient completely stopping their participation in **ANY** Part of the study – Part 1, Part 2 Intervention Phase or Part 2 Follow-Up Phase Patients who **withdraw** at any stage will **completely exit** the study and will **NOT** undertake any further data collection.

Discontinuation – relates to a patient stopping their participation in Part 2 – Intervention Phase earlier than planned **BUT** proceeding to Part 2 - RCT: Follow-Up Phase.

Withdrawing or discontinuing participation will not affect a patient's future treatment or care.

During **Part 1**, a patient can **withdraw/be withdrawn** for the following reasons:

1. Withdrawal of consent
2. Death
3. Patient becomes ineligible (see Inclusion/Exclusion Criteria Sections 8.3, 8.4)
4. Inability to continue participation due to loss of physical or mental capacity
5. Inability to obtain mobile phone signal in order to ensure patient safety
6. A device-related incident (see Section 12.2.1)

During Part 1, if a patient **withdraws/is withdrawn** prior to participation, they will be considered as a screen failure. Screen failures will be replaced, but also recorded in a feasibility evaluation pro-forma for consideration prior to proceeding to Part 2. If a patient withdraws/is withdrawn during participation in Part 1, data already collected in relation to the patient may be retained and used for the purposes for which consent has already been given.

During **Part 2 – Intervention Phase**, a patient can **withdraw/be withdrawn** for the following reasons:

1. Withdrawal of consent
2. Death
3. Patient becomes ineligible (see Inclusion/Exclusion Criteria Sections 8.3, 8.4)
4. Inability to continue participation due to loss of physical or mental capacity
5. Inability to obtain mobile phone signal in order to ensure patient safety (only applicable to Intervention Group during RCT Intervention Phase)

A patient should be **discontinued** for the following reason:

6. Chemotherapy cessation or treatment change to non-chemotherapy treatment
7. A change from a 2, 3 or 4 weekly chemotherapy treatment to a weekly chemotherapy treatment

A patient should be either **withdrawn or discontinued** for a:

8. Device–related incident (see Section 12.2.1)

During Part 2- Intervention Phase, if a patient **withdraws/is withdrawn** prior to randomisation to study condition, they will be considered as a screen failure. Screen failures will be recorded by the research nurse/assistant/designated health professional and also replaced to ensure that 1,108 patients are randomised in Part 2: Intervention Phase. If a patient **withdraws/is withdrawn** after randomisation to study condition has taken place and data collection has begun, data already collected in relation to the patient may be retained and used for the purposes for which consent will have already been given. Attrition rates during Part 2: Intervention Phase have been taken into consideration to ensure that statistical power of the study is maintained (Section 13.3.2).

Patients who **discontinue** their participation during the Intervention Phase of Part 2 will proceed immediately to the Follow-Up Phase and will be treated as full study participants. If a patient who has been discontinued does not wish to participate in the Follow-Up Phase, this will be marked as 'withdrawal of consent'.

During **Part 2 – Follow-Up Phase,** a patient may **withdraw/be withdrawn** for the following reasons:

1. Withdrawal of consent
2. Death
3. Inability to continue participation due to loss of physical or mental capacity

For both Parts 1 and 2, the reason for withdrawal/discontinuation will be recorded on the electronic-Case Report Form (e-CRF). The local clinical site will be responsible for reporting the reason for withdrawal/discontinuation to the local site PI as soon as possible. The local clinical sites will also be responsible for reporting reasons for any **withdrawn** or **discontinued** patient to the Chief Investigator during regular accrual/attrition updates.

9 STUDY PROTOCOL

9.1 Study Procedures

9.1.1 Study Conduct

The study will be conducted in two parts, and will be run by the University of Strathclyde's Department of Information and Computing Sciences in conjunction with Surrey Clinical Research Centre (CRC), which has experience of running other FP7 EU trials. This study will be conducted in accordance with the principles set out in the Declaration of Helsinki (1989).

The study will commence in each country after a favourable opinion has been obtained from an independent Ethics Committee, and the study has been given NHS (R&D) approval (or equivalent) in the relevant country. Written informed consent will be obtained after a patient is informed of the nature, significance, implications and risks of the study and prior to the commencement of any study specific procedures.

9.1.2 Patient and Clinician Advisory Groups

Throughout the study, voluntary patient and clinician advisory groups will be convened within each participating country to inform its conduct. Representation will include people with breast

cancer, colorectal cancer, HD or NHL. Clinical groups will consist of specialist nurses, breast and colorectal oncologists, haematologists and other related health care professionals. In addition specialists from supportive care will also be involved to ensure the wider aspects of patient support are addressed.

The aim of the patient and clinical advisory groups will be to work effectively with patients, clinicians, ECPC and other voluntary cancer organisations to ensure that the study conduct is in line with key users' perspectives, experiences and needs, and informed by the best available clinical evidence and expertise, throughout the life time of the project.

9.1.3 Part 1: Preparation of the ASyMS intervention for use in a European setting

Part 1 will entail the following:

9.1.3.1 Review of clinical guidelines for the assessment and management of chemotherapy-related toxicity

A scoping review of the literature and international, national and local guidelines relative to the assessment and management (professional and self-care) of chemotherapy-related toxicity will be conducted to ensure that the ASyMS technology reflects current evidence and local practice. Briefly, this review will follow the framework of scoping reviews established by Arksey and O'Malley [43]. Once the research questions will be finalised, a systematic literature search strategy will be devised and run in three electronic databases (PubMed, CINAHL and PsycARTICLES) using Boolean operators, truncation markers and MeSH headings. The search strategy, comprising of five search strings, will be created using a combination of key words, phrases and synonyms. All searches will be limited to English papers, studies with human participants, with an abstract available dating from January 2004 to April 2014.

9.1.3.2 Refinement of risk algorithms for symptom alerts

The content of the existing system was rigorously developed via systematic reviews of the literature and expert clinician consensus in the UK and Australia in 2011. Based on this extensive work and previous experience, significant changes to the ASyMS technology are not expected. However, in order to ensure that the intervention is suitable for use in various European contexts, all information will be updated and reviewed by health professionals at the participating sites to ensure that the system reflects international, national and local practice policies.

9.1.3.3 Standardisation of responses to symptom alerts

Following the scoping review outlined above, all symptom management interventions (including responding to and handling symptom alerts) and self-care advice directed to patients using the ASyMS technology (Part 1 or Part 2) will be standardised across all clinical sites. It is expected that standardisation of any symptom management interventions and self-care advice will prevent bias from interfering with the effectiveness of the ASyMS technology on patient outcomes due to significant differences in the patterns of clinical responses to symptoms across the different clinical sites and across the different countries.

9.1.3.4 Translation and cultural adaptation of study components

The multi-national nature of this study renders necessary the use of different language versions of all study components in the partner countries. The goal of this procedure will be to document that each translation adequately captures the concepts of the original English-language version of each component and is readily understood by end users in the target population. This will

be a crucial step to ensure equivalence of different versions that can enable successful aggregation of multinational datasets [44].

Specifically, for those PROMs for which a validated version in the respective language does not exist, the original English version will be translated and culturally adapted in the respective language. According to the US Food and Drug Administration, where language translations of PROMs or additional study components are required, these should be undertaken in ways that show evidence that the content validity and other measurement properties of the PROM remain equivalent to those of the original version [45]. Therefore, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has recently published key documents detailing areas designed to maintain content integrity during translation procedures [44, 46]. These areas refer to the requirement for (a) a rigorous translation protocol to ensure content equivalence between the original and translated versions of a PROM or other component, and (b) a linguistic/contextual validation protocol usually involving cognitive debriefing with patients to confirm that the translated version is well understood by key end users. eSMART will follow this process.

Independent translation companies will undertake translation of additional components, including the eSMART website, the ASyMS website, and economic evaluation outcome measures. Translation of supporting documentation including information sheets, consent forms, study pro-formas, and interview guides will be the responsibility of members of the eSMART consortium.

9.1.3.5 Deployment of the ASyMS technology

During Part 1, key aspects for the deployment of the ASyMS technology will be evaluated in preparation for Part 2. A structured survey will be completed at each participating site detailing factors such as mobile phone coverage, available local networks, Wi-Fi coverage and current internet operating systems. In addition, live testing will be conducted to assess mobile phone coverage for the clinical areas in which the ASyMS technology will be used. Poor areas of coverage will be identified and appropriate solutions provided. The ASyMS technology has been developed to work with basic health IT infrastructures; therefore, no major technological changes are anticipated. Based on previous experience, corrective actions that may be required at this stage may include the purchase of additional computers for staff within the clinical area and updating browser software versions.

9.1.3.6 Feasibility Testing Period

Following the preparatory work period, the ASyMS technology will be tested by up to 6 patients per site, i.e. *n*=2 per cancer type depending on the different cancer types being evaluated at each site (max. n=6 per participating site), over one CTx to ensure that possible issues/problems with the technology identified by the local site PIs and/or research nurses/assistants are tackled prior to full deployment in Part 2.

9.1.3.6.1 Research design

Descriptive, single-arm, prospective, observational.

9.1.3.6.2 Procedures

Based on pre-specified eligibility criteria (see Section 8), patients diagnosed with breast cancer, colorectal cancer, HD or NHL will be invited to use the ASyMS intervention once daily and any time they feel unwell over one full CTx (1st day of a given CTx until the 1st day of the next CTx) during chemotherapy treatment. Patients will be allowed to enter the feasibility testing period at any point during active chemotherapy, thus allowing for diversity in the CTx where the patients will be called to use the technology.

All consenting patients will provide written informed consent. Patients who refuse participation will be thanked for their time and reassured that their decision will in no way compromise their rights and standard of care they receive. Whilst provision of a reason for refusal will not be mandatory, patients will be asked to provide a reason if they so wish; reasons for refusal will be recorded by the research nurse/assistant/designated health professional.

Up to 6 patients per site, i.e. *n*=2 per cancer type depending on the different cancer types being evaluated at each site (max. n=6 per participating site) will be approached by members of the local clinical team and invited to take part in the feasibility testing period.

A number of parameters will be evaluated, including assessing the technological readiness of the system such as training of patients/staff, patient and clinician registration on the system, data transfer from patient handset to the study server, clinician access to the ASyMS web portal, ability of clinicians to deal with alerts and log on/use nurse handset for the receipt of alerts, technological connectivity, completion of ePROMs (pre-CTx and mid-CTx assessments) and transfer to the study server, completion of electronic clinical and demographic patient data and successful transfer to the study server and completion of electronic case note reviews.

9.1.3.6.2.1 Patient Screening

Each study partner (co-investigator) in the participating countries will be working closely with colleagues within the local clinical team at each of the participating sites. A clinical site-specific PI (local site PI) will be identified at each participating site, who will be liaising directly with the study partner. In certain cases, study partners will also be the local site PIs.

Eligible patients will be identified by local site PI or other members of the local clinical team at each participating site, and recruited from out-patient and/or in-patient oncology clinics at the start of any CTx during chemotherapy treatment for the first time.

9.1.3.6.2.2 Patient Recruitment

Members of the local clinical teams (i.e. medical and/or nursing staff) and/or dedicated research assistants/research nurses will assist in the recruitment of patients at each of the participating sites.

Once an eligible patient is identified, a member of the clinical/research team will briefly introduce the study to the patient through use of a Top 10 Facts about eSMART information sheet/ patient information sheet. Patients interested in hearing more about the study will be spoken to further by the research nurse/assistant/designated health professional, to enable patients to have the opportunity to ask questions, and have these questions sufficiently answered to ensure that patients will be providing informed consent. Patient contact information will be recorded at this stage by the research nurse/assistant with the patient's verbal consent. Patients will be given a sufficient period of time to consider participation and they will be advised that they can discuss the study with any significant others and/or health professionals prior to making a final decision. If the patient wants to participate and feels able to give their consent at this time then they will be asked to sign the necessary documentation at this time and arrangements will be made to collect baseline information. If the patient feels they want to take some more time to consider their participation, the research nurse/assistant/designated health professional will contact the patient at a mutually convenient time over the next few days to confirm whether or not they would be willing to take part in the study. If patients agree to the study, they will be asked to attend the clinic prior to their pre-arranged appointment for chemotherapy administration (baseline visit). Patients who refuse participation will be thanked for their time and again reassured that their decision will in no way compromise their rights and standard of care they will receive. Whilst provision of a reason for refusal will not be mandatory, those patients will be asked to provide a reason if they so

wish; reasons for refusal will be recorded by the research nurse/assistant/designated health professional.

During the baseline visit, consenting patients will be asked to sign three copies of the informed consent form. One copy will be given to the patient to keep, one copy will be inserted in the patient's case notes, and one copy will be securely archived by the research nurse/assistant in the local study site file.

During the baseline visit, consenting patients will also be asked to first complete a set of the study ePROMs on a tablet PC or PC and then trained to the use of the ASyMS technology prior to commencement of their participation. In addition, all consenting patients will be registered by the research nurse/assistant/designated health professional on the ASyMS web-based system. The research nurse/assistant/designated health professional will use their own, unique username and password to have access to the web-based system.

9.1.3.6.2.3 Patient training on the intervention

See below in this Section (Part 2).

9.1.3.6.2.4 Clinician training on the intervention

See below in this Section (Part 2).

9.1.3.6.2.5 Patient participation and data collection

Patients will be required to engage in the actions described in Section 10 for patients allocated to intervention group.

All participants will be required to complete a set of ePROMs (primary and secondary) at baseline (i.e. prior to next CTX), at mid-CTx (where appropriate) and around the start of the subsequent CTx (between 2 days before and 1 day after chemotherapy administration).

PROM data will be collected either in the hospital, where patients will be asked to use a tablet PC or PC each time they are required to complete the ePROMs or if they prefer via a link sent to their personal email. Where required, the research nurse/assistant/designated health professional will be assisting patients to enter information on the tablet PC or PC. The tablet PC or PC will securely hold electronic versions of the PROMs questionnaires, allowing data to be transferred to a secure Good Clinical Practice (GCP)-compliant database.

Figure 3 provides a schematic of all procedures during the feasibility testing period in Part 1.

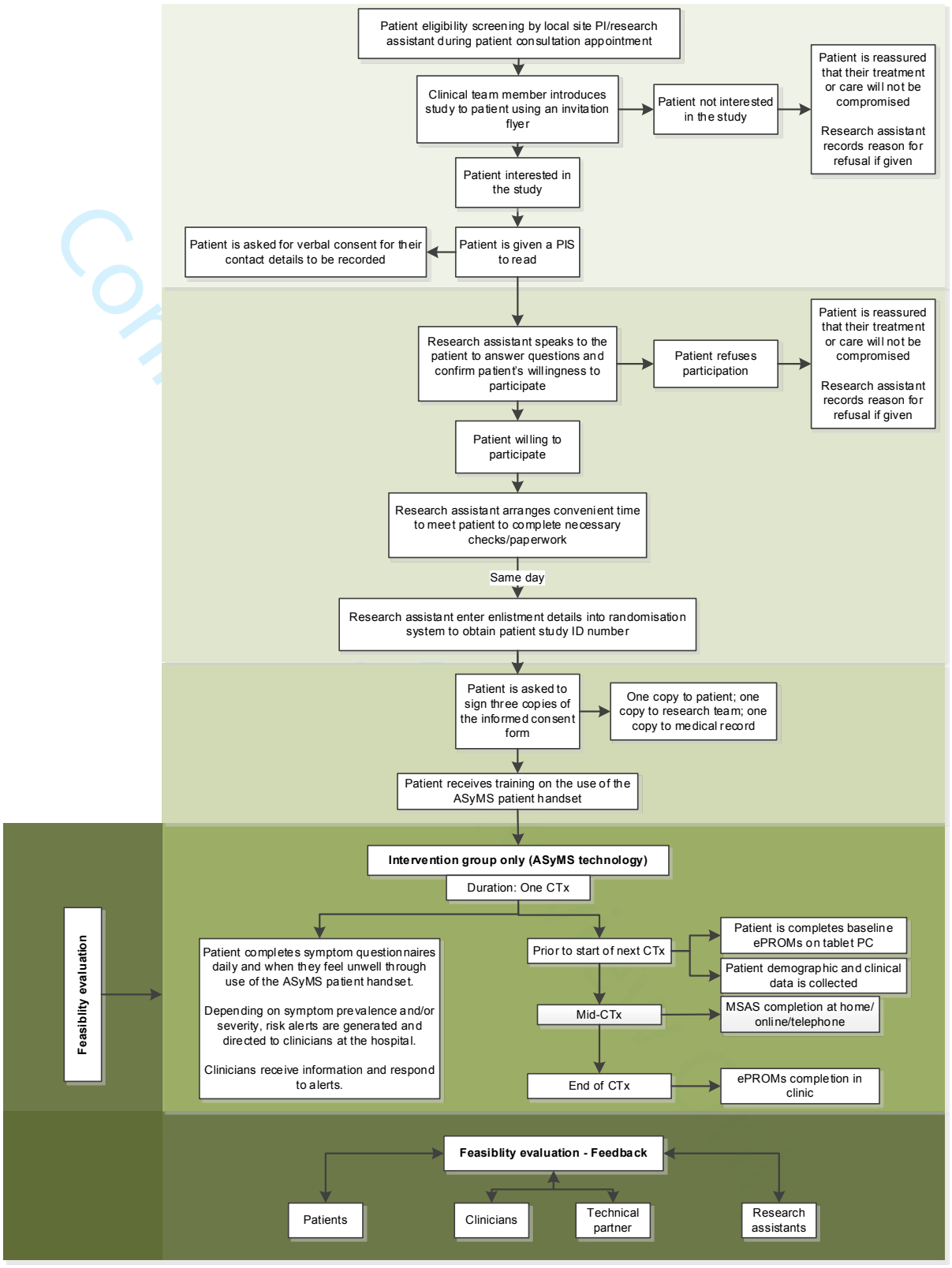

Figure 3. Schematic of procedures during the feasibility testing period (Part 1). *Notes* – CTx: Chemotherapy cycle; Mid-CTx: Mid-cycle assessment.

9.1.3.7 Evaluation of feedback from feasibility testing period prior to RCT

All feedback received during the feasibility testing period will be analysed (see Section 13) to inform the course of action to be taken prior to full deployment of ASyMS during the RCT (Part 2). This will involve reviewing and potentially revising the approach to patient/staff training to use ASyMS, patient and clinician registration on ASyMS, use of patient handset, transfer of data from patient handset to study server and technological connectivity issues to reduce potential risk, clinician access and log onto the ASyMS web portal to ensure timely and problem-free access, ability of clinicians to deal with an alert using the ASyMS web portal, ability of clinicians to log on and use ASyMS nurse handset for the receipt of alerts, completion of ePROM data by patients and successful transfer to study server, completion of electronic clinical and demographic patient data and successful transfer to the study server, and completion of electronic case note reviews and successful transfer to the study server. In response to identified problems, necessary actions will be taken to prevent patient/clinician burden, reduce patient risk due to technology loss, malfunction or damage, increase patient/clinician adherence to study procedures, and ensure seamless communication between patients and clinicians, and patients, clinicians and support.

All clinical sites that meet the afore-mentioned requirements will proceed to Part 2 of the project.

In those clinical sites where all or part of the afore-mentioned requirements are not met, every effort will be made for issues to be resolved during Part 1.

Where however, despite all efforts to meet the afore-mentioned requirements, issues remain unresolved thus posing a risk to the project's conduct, clinical sites will be excluded. Excluded clinical sites will be replaced or, if this proves challenging or not feasible, recruitment of patients will be re-allocated to the remaining participating clinical sites.

9.1.3.8 Evaluation of current clinical practice prior to RCT

To explore and understand how care is organised in relation to symptom management both during and out of hours prior to the introduction of the ASyMS intervention, symptom management protocols will be examined at each clinical site within each country and for each patient diagnostic group, where relevant. Reviewing these documents will allow for relevant data to be extracted about how key symptoms are currently managed and how adverse events are managed.

In addition, a baseline Assessment of Changes in Clinical Practice questionnaire will be issued to all sites in all countries via an online survey tool. This questionnaire will gather information regarding current patient pathways and processes of care for the management of chemotherapy related toxicities. This questionnaire will gather information on resources used relative to the management of chemotherapy toxicities, including staff grades, time taken to deal with the toxicities of treatment, healthcare resources used, and settings in which care is delivered.

Up to 20 nursing, medical, pharmacy and audit/data management staff will be asked to complete this questionnaire at each site. Data gathered from these questionnaires will be mapped against the data extracted from the symptom management protocols to help illustrate and understand the ways in which chemotherapy toxicity is managed at each of the sites, prior to the introduction of the ASyMS technology within the RCT.

9.1.4 Part 2 – Pre-trial participation

9.1.4.1 Patient Screening

Each study partner (co-investigator) in the participating countries will be working closely with colleagues within the local clinical team at each of the participating sites. A clinical site-specific PI (local site PI) will be identified at each participating site, who will be liaising directly with the study partner. In certain cases, study partners will also be the local site PIs.

Eligible patients will be identified by local site PI or other members of the local clinical team at each participating site, and recruited from out-patient and/or in-patient oncology wards prior to the commencement of chemotherapy treatment for the first time.

9.1.4.2 Patient Recruitment

Members of the local clinical teams (i.e. medical and/or nursing staff) and/or dedicated research assistants/research nurses/designated health professionals will assist in the recruitment of patients at each of the participating sites.

Once an eligible patient is identified, a member of the clinical/research team will briefly introduce the study to the patient through use of a Top 10 Facts about eSMART information sheet/patient information sheet. Patients interested in hearing more about the study will be spoken to further by the research nurse/assistant/designated health professional, to enable patients to have the opportunity to ask questions, and have these questions sufficiently answered to ensure that patients will be providing informed consent. Patient contact information will be recorded at this stage by the research nurse/assistant/designated health professionals with the patient's verbal consent. Patients will be given a sufficient period of time to consider participation and they will be advised that they can discuss the study with any significant others and/or health professionals prior to making a final decision. If the patient wants to participate and feels able to give their informed consent at this time then they will be asked to sign the necessary documentation at this time and arrangements will be made to collect baseline information. If the patient feels they want to take some more time to consider their participation, the research nurse/assistant/designated health professional will contact the patient at a mutually convenient time over the next few days to confirm whether or not they would be willing to take part in the study. If patients agree to the study, they will be asked to attend the clinical site prior to their pre-arranged appointment for chemotherapy commencement (baseline visit). Patients who refuse participation will be thanked for their time and again reassured that their decision will in no way compromise their rights and standard of care they will receive. Whilst provision of a reason for refusal will not be mandatory, those patients will be asked to provide a reason if they so wish; reasons for refusal will be recorded by the research nurse/assistant/designated health professional.

During the baseline visit, consenting patients will be asked to sign three copies of the informed consent form. One copy will be given to the patient to keep, one copy will be inserted in the patient's case notes, and one copy will be securely archived by the research nurse/assistant in the local study site file.

Following the patient's written consent, the research nurse/assistant/designated health professional will enter enlistment details in an eCRF to obtain a patient study ID number and randomisation group. This allocation will also determine whether the participant has been allocated to the mid-CTx measurement (30% of total study sample).

Consenting patients will be asked to first complete a set of the study ePROMs on a tablet PC or PC. If patients are allocated to the intervention group, the research nurse/assistant will offer a brief overview of study procedures as already discussed during consent, and then train the patient to the use of the ASyMS technology prior to commencement of chemotherapy. If patients are allocated to the control group, the research nurse/assistant will offer a brief overview of study procedures as already discussed during consent.

9.1.4.3 Patient Training/Education

Irrespective of study condition allocation, all consenting patients will be asked to attend the clinical site to their pre-arranged appointment to commence chemotherapy treatment. At this time, the research nurse/assistant/designated health professional will meet the patient, obtain written informed consent and perform training with the patient depending on allocation to study condition.

9.1.4.3.1.1 Patient training (intervention group)

On registration, patients allocated to the intervention group will be provided with a mobile phone (i.e. ASyMS patient handset) and a tympanic thermometer. The research nurse/assistant will then instruct them on how to use the ASyMS patient handset to complete an electronic ASyMS symptom questionnaire (i.e. Chemotherapy Toxicity Self-Assessment Questionnaire, CTAQ) by entering symptom/temperature data, and also receive self-care information. A manual for the ASyMS patient handset containing instructions and contact numbers will also be given to each participant. Patients will be educated about the additional features within the ASyMS patient handset, and these include: the self-care library, patient symptoms graphs, and how to view text messages sent to them from their clinical team. During patient training (i.e. prior to their next CTx), patients will be asked to complete the ASyMS symptom questionnaire on their handset, take their temperature and send this information to the study server. If the patient experiences any problems with this procedure, further training will be conducted until the patient feels comfortable using the ASyMS patient handset and they can successfully transmit their symptom information from the ASyMS patient handset to the study server when at home. In any case, in the interest of patient safety, patients who will be using the ASyMS intervention will be reminded that in cases where a failure in the technology occurs, standard care will apply throughout their participation in the study. Also, all patients will receive contact details in the event of a problem with their participation in the study (provided in the patient information sheet).

In addition, all patients in the intervention group will be informed about data collection procedures as detailed in Section 9.1.5.2.

9.1.4.3.1.2 Patient training (control group)

On registration, patients allocated to the control group will be informed about data collection procedures as detailed in Section 9.1.5.2.

9.1.4.4 Clinician Training on the Intervention

Dedicated training sessions with members of the local clinical team (local 'alert handlers') will take place prior to commencement of patient recruitment to Part 2. All local 'alert handlers' will be registered on the ASyMS website and go through a detailed, step-by-step educational process regarding how to receive (i.e. be notified of the alert through use of the ASyMS clinician handset), review (i.e. access information on the ASyMS clinician handset and on the ASyMS website) and respond to an alert by accessing information on the ASyMS website, calling the patient at home or on the patients' mobile phone, performing a clinical assessment, documenting all actions/interventions, and signing off the alert. A manual for the ASyMS clinician handset and the ASyMS website containing instructions and details of the web based support system will also be given to each local clinical team. During clinician training, a hands-on demonstration using fictitious data to create alerts and access a training version of the ASyMS website will be performed. If clinicians experience any difficulties with this procedure, further training will be conducted until the clinician feels comfortable and confident in using the ASyMS clinician handset and navigating around the ASyMS website to deal with an alert. In the interest of patient safety, clinicians will be reminded that in cases where a failure in the technology occurs, standard care will apply for patients in the intervention group throughout their participation in the study.

9.1.5 Part 2 – RCT: Intervention Phase

9.1.5.1 Research Design

Repeated-measures, parallel-group stratified RCT.

9.1.5.2 Procedures

Depending on study condition allocation, participants will be required to engage in the actions described in Section 10 during the active treatment period.

Irrespective of study condition, all participants will be asked to complete a set of ePROMs (primary and secondary) at baseline (i.e. prior to first CTx) and at the end of each cycle of chemotherapy (between 2 days before and 1 day after chemotherapy administration) up to a maximum of 6 cycles of chemotherapy. In addition, a subsample of randomly selected patients from the intervention and control groups will be asked to complete a mid-CTx measurement of the primary outcome measure (i.e. MSAS) at each CTx in order to capture additional data on symptom burden at this time. Depending on the duration of a given CTx (based on the specific chemotherapy treatment) and patient availability, patients will be asked to complete the mid-CTx assessment between day 6 and day 8 for 2-weekly treatments, between day 9 and day 11 for 3-weekly treatments, and between day 13 and day 15 for 4-weekly treatments.

PROM data will be collected either in the hospital, where patients will be asked to use a tablet PC or PC each time they are required to complete the ePROMs or if they prefer via a link sent to their personal email. Where required, the research nurse/assistant will be assisting patients to enter information on the tablet PC or PC. The tablet PC or PC will securely hold electronic versions of the PROMs questionnaires, allowing data to be transferred to a secure GCP-compliant database. During active chemotherapy (for up to a maximum of 6 cycles of chemotherapy), the data collection will coincide with visits to receive their next CTx.

For the sub-set of patients completing the mid-CTx MSAS (for up to a maximum of 6 cycles of chemotherapy), measurements will be conducted through a telephone interview/secure web link with the research nurse/assistant/designated health professional while the patient is at home. During this mid-CTx measurement, the research nurse/assistant/designated health professional will record patient responses on the MSAS items on the same tablet PC or PC that will be using for patient self-reported data collection. During this mid-CTx measurement, the research nurse/assistant/designated health professional will not provide any symptom-related advice to patients so as to avoid positively or negatively affecting any trial intervention effects.

At the end of their 6th cycle of chemotherapy (or sooner if a patient receives fewer than 6 cycles of chemotherapy), patients will move from the Intervention Phase into the Follow Up Phase of the study. Patients will complete the ePROMs at the end of this cycle of chemotherapy and this set of PROMs (known as the Transition ePROMs) will be used as both the end measurement for the Intervention Phase and the baseline measurement for the Follow Up Phase. This ePROMs MUST be completed **within 5 calendar days** of the patient completing their 6th (or earlier) cycle of chemotherapy. Patients can complete this ePROMs either on the tablet/PC in the hospital or at home via the secure link sent to their personal email.

Figure 4 provides a schematic of all data collection time-points and procedures during the Intervention Phase.

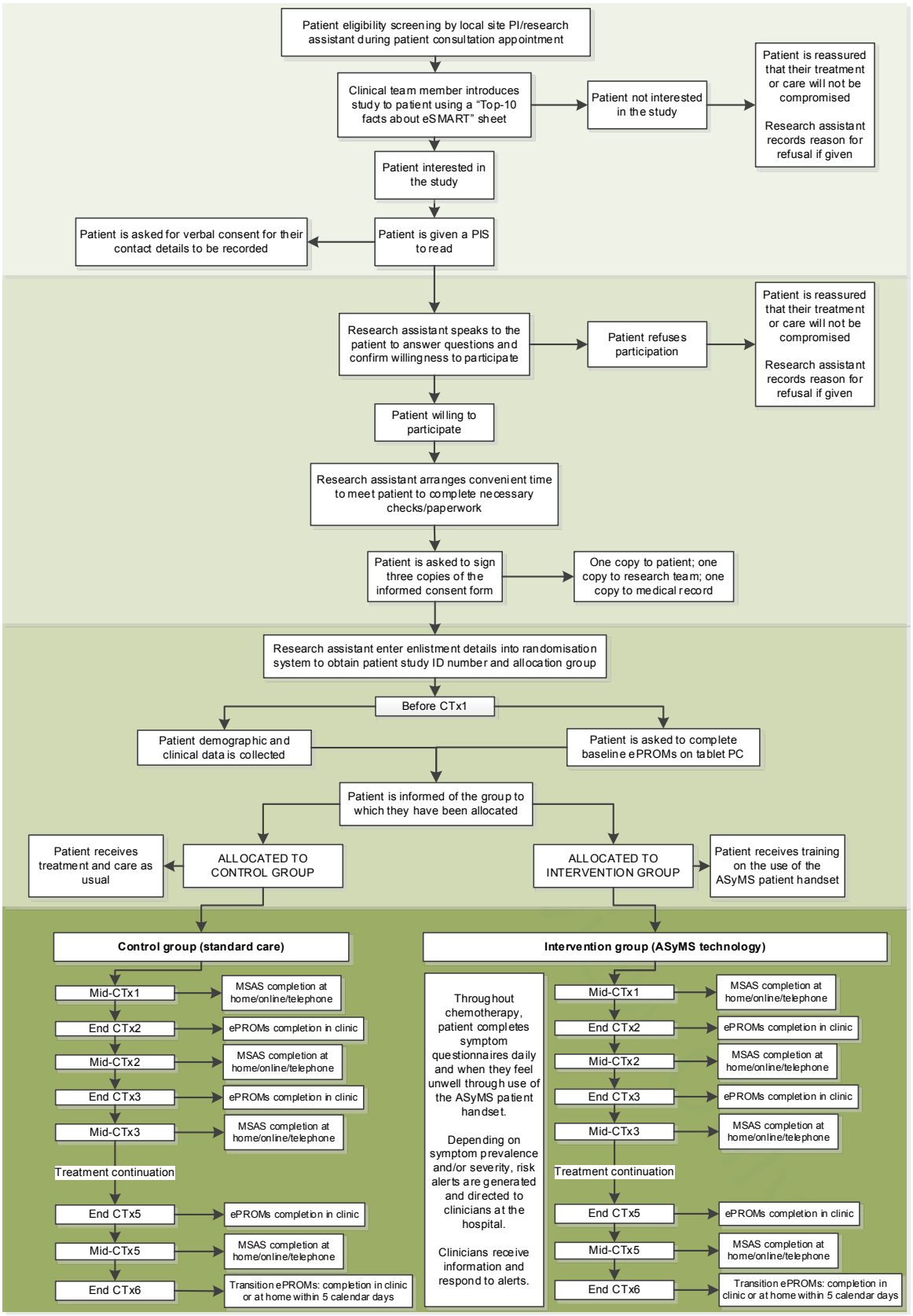

Figure 4. Schematic for data collection time-points (example for patient completing all 6 CTx) and procedures during the intervention phase (Part 2). *Notes* - CTx: Chemotherapy cycle; Mid-CTx: Mid-cycle assessment.

9.1.6 Part 2 – RCT: Follow-up Phase

9.1.6.1 Research Design

Repeated-measures cohort involving two separate groups of patients (previously identified as intervention and control).

9.1.6.2 Procedures

On completion of a maximum of 6 cycles of chemotherapy, patients in the intervention group will be asked to return all equipment (i.e. the ASyMS patient handset and the tympanic thermometer). Patients from the intervention group who continue to receive chemotherapy treatment during the Follow-Up Phase will be advised that, as they no longer have the mobile phone, they should now follow the normal standard care procedures of their clinical site. Both the intervention and the control group will be followed-up for up to one year following a maximum of 6 cycles of chemotherapy to evaluate sustainability of the intervention effects.

Follow-up data collection will take place at pre-specified time-points every 3 months for up to a maximum of one year. A The 'baseline assessment' for the Follow Up Phase (known as the Transition ePROMs) will take place **within 5 working days** of the end of the patient's 6th cycle of chemotherapy (or earlier if they are receiving fewer than 6 cycles). Subsequent assessments will take place at 3 monthly intervals for up to 12 months. Prior to each follow up assessment, the research nurse/assistant will check the hospital's records and, if required, contact the patient's GP/oncology consultant/family physician (NB. only if the patient has given written consent for their GP/oncology consultant/family physician to be contacted) to verify the patient's health status, e.g. cancer relapse or death. If the patient is alive and still eligible for participation in the study, he/she will then be contacted for their next scheduled assessment. If the patient is not alive or has become ineligible, then all scheduled assessments will be suspended and patient participation will be terminated.

A sequential mixed-mode design for data collection will be used to allow for flexibility in data collection and control for non-respondent follow-up. PROM data will be collected in the hospital, where patients will be asked to use a tablet PC or PC each time they are required to complete the ePROMs. Where required, the research nurse/assistant will be assisting patients to enter information on the tablet PC or PC. If data cannot be collected in clinics (using the afore-mentioned PC tablets), two alternative options will be given to patients:

1. Data collection through internet surveys (sent via personalised e-mails) with telephone follow-up to non-responders.
2. Data collection through telephone-conducted interviews completed by research nurses/assistants, who will then enter data onto tablet PC or PC.

The use of sequential mixed-mode design for non-respondent follow-up may enhance perceptions of the importance of the research/ increase response, be cost effective and reduce non-response bias with minimal effect on data quality [47]. This approach may reduce costs and non-response bias with minimal effect on data quality. Patients will be asked about their preferred mode of follow-up at the end of the active treatment period and before the follow-up period commences.

At the final data collection for Part-2 RCT: Follow-Up Phase the research nurse/assistant will enter data about the patients' cancer-related treatment and health during the follow-up period onto the online study database. After the final data collection for the Part 2- RCT: Follow-Up Phase a thank you letter will be sent to all participants.

Figure 5 provides a schematic of all data collection time-points and procedures during the one-year follow-up phase.

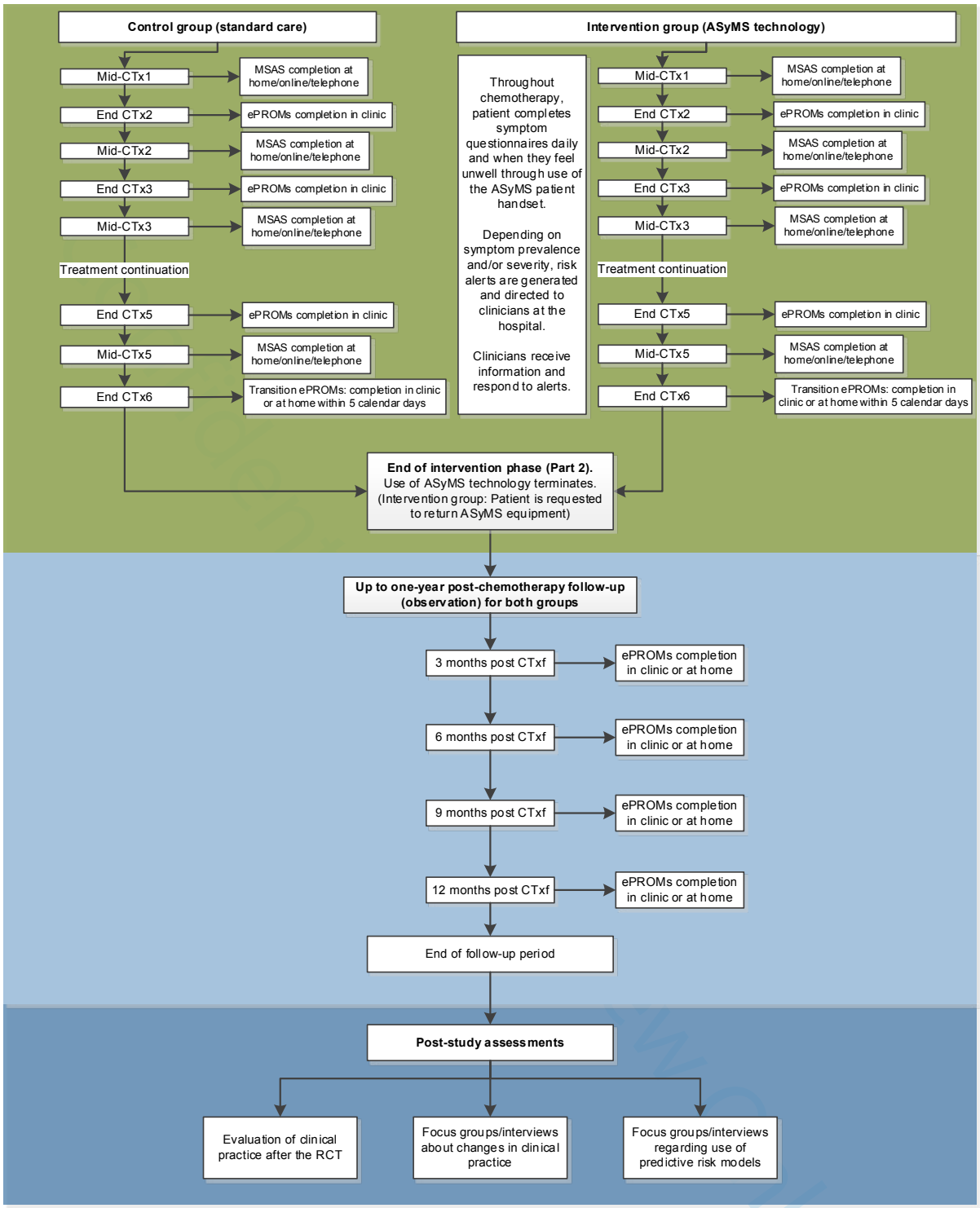

Figure 5. Schematic of data collection time-points and procedures for a patient receiving one-year follow-up during post-intervention period (Part 2). *Notes* – Follow-up assessments will be conducted at 3-monthly intervals for up to a maximum of 12 months. Assessments will be conducted either in clinic (in-person completion of ePROMs on tablet PC) or at home (through either e-mail invitation or telephone interview)

9.1.7 Part 2 – Development and Testing of PRMs

The development of PRMs will be achieved in tandem with the on-going RCT. The PRMs developed will combine clinical, demographic, social, and health service data collected from previous studies, as well as the current study, to inform the predictions made, thus facilitating delivery of care that is individualised and encompasses several important domains of the patient's experience. Furthermore, in the development of the PRMs, particular attention will be paid to evaluate the effects of gender and age on the occurrence and severity of chemotherapy-induced toxicities.

Specifically, data will be analysed from previous studies conducted by eSMART partners as well as data collected as part of the eSMART study to develop the initial PRMs. The data on patients with breast and colorectal cancer were collected from patients receiving cancer chemotherapy who were enrolled in studies funded by the National Cancer Institute in the United States and Burdett Trust for Nursing, Macmillan Cancer Care, Scottish Government and Philips HealthCare in the United Kingdom. Both studies were approved by the Committee on Human Research at each of the Principal Investigators' research institutions before any data collection commenced. All of the patients in these studies signed written informed consent to have their responses to questionnaire booklets used for symptom management research studies. All of the data will be de-identified prior to being used in any of the analyses listed below, and will be kept on a secure server. Only investigators directly involved in this project will have access to these data.

Because the development of these predictive risk models is exploratory in nature, a variety of statistical procedures will be used to determine the best fitting models. Two sets of PRMs will be developed: one set derived using standard mathematical modelling (utilising techniques such as logistical regression, latent growth curve analysis, hierarchical linear modelling, reasoned modelling, Bayesian inference and curve fitting) and the other developed using machine learning (including neural networks and evolutionary algorithms).

The sets of models will then be combined, resulting in 3 hybrid PRMs, one each for use in modelling symptoms in people with breast, colorectal and haematological cancers, respectively.

9.1.8 Part 2 – Post-trial Assessments

9.1.8.1 Assessment of Changes in Clinical Practice following the RCT

To explore and understand how care is organised in relation to symptom management both during and out of hours following the introduction of the ASyMS technology, a follow-up Assessment of Changes in Clinical Practice Questionnaire will be issued to all sites in all countries via an online survey tool. This questionnaire will gather information regarding patient pathways and processes of care for the management of chemotherapy related toxicities, following the introduction of the ASyMS Technology. The questionnaire will gather information on resources used relative to the management of chemotherapy toxicities, with a particular focus in this follow-up period on patients who used the ASyMS intervention. Similar to the baseline questionnaire, the follow-up Assessment of Changes in Clinical Practice Questionnaire will include staff grades, time taken to deal with the toxicities of treatment, healthcare resources used, and settings in which care is delivered.

Up to 20 nursing, medical, pharmacy and audit/data management staff will be asked to complete this questionnaire at each site. Data gathered from these questionnaires will be statistically compared and contrasted and mapped against the data extracted from the symptom management protocols and the data from the baseline Assessment of Changes in Clinical Practice Questionnaire to help illustrate and understand the ways in which chemotherapy toxicity is managed at each of the sites, following the introduction of the ASyMS technology.

9.1.8.2 Telephone/face-to-face interviews/focus groups about changes in clinical practice

In addition to the follow-up Assessment of Changes in Clinical Practice Questionnaire, following the completion of the RCT, telephone/face-to-face interviews/focus groups with clinical staff will be conducted at each site to further explore, understand and gain perspectives of any changes in care as a result of the ASyMS intervention. Up to 10 members of the clinical team will be asked to participate in telephone/face-to-face interviews/focus groups at each site. The telephone/face-to-face interviews/focus groups will be conducted by members of the collaborative research team and/or by research nurses/assistants/designated health professionals at each site (training will be received by all interviewers/focus group facilitators prior to conducting any telephone/face-to-face interviews/focus groups). Telephone/face-to-face interviews/focus groups will be recorded, transcribed verbatim in native language (where not conducted in English) and translated to English where necessary and appropriate. Data gathered from the telephone/face-to-face interviews/focus groups will be mapped against and compared to the data gathered from the Assessment of Changes in Clinical Practice Questionnaires. Further, the telephone/face-to-face interviews/focus groups will allow for possible differences in practices across the sites to be identified and will provide opportunity to further understand why these differences have emerged. Finally, the telephone/face-to-face interviews/focus groups will also provide opportunity to consider any common conditions across the sites, which is important in the context of the improvement of services.

Patients' perspectives of changes in clinical practice will also be explored through the use of interviews (either face-to-face or telephone)/focus groups. Up to 5-10 patients from the Intervention Group per location will be asked, either during or around their completion of the Intervention Phase, to take part in an interview (either face-to-face or telephone)/focus group to explore their experiences of clinical care and technology. A process of maximum variation sampling around age, gender and diagnosis will be used to ensure as representative a sample as possible. Interviews (either face-to-face or telephone) or focus groups will be conducted in the patients' preferred language. An interview schedule, underpinned by a theoretical framework, such as the Technology Acceptance Model, will be developed and used by those responsible for conducting the interviews or focus groups. Interviews/focus groups will be recorded and transcribed (and translated if necessary) for thematic analysis.

9.1.8.3 Focus groups/interviews regarding use of PRMs

In addition to the above, two focus groups/interviews with patients (n=1) and clinicians (n=1) will be conducted in each country to explore their perceptions of the utility of the PRMs in clinical practice and in their ability to provide relevant information to inform the delivery of a preventative and anticipatory model of care. All potential participants will be consented to these focus groups/interviews through use of focus groups/interviews -specific patient information sheets and informed consent forms. Interview guides will be devised and used to help direct the conversation towards the topics of interest.

At these focus groups/interviews the investigators will ask the patients and clinicians about the perceived utility of the PRMs in clinical practice and in their ability to provide relevant information to inform the delivery of a preventative and anticipatory model of care. The focus groups/interviews will be conducted by members of the collaborative research team and/or by research nurses/assistants/designated health professionals. The focus groups/interviews will begin by explaining the purpose of the meeting and asking all participants to sign the consent form. Focus group/interviews attendees will be informed that all of the comments in the focus group will be reported in the aggregate. None of the participants in the focus groups/interviews will be identified by name. Following this introduction, the investigators will share the PRMs with the focus group/interviews attendees. Participants will be encouraged to provide their feedback on PRMs in terms of their usefulness for clinical practice. It is anticipated that the focus groups/interviews will last approximately 60 minutes.

It should be noted that for pragmatic reasons, the same clinicians may be asked to take part in two focus groups/interviews (i.e. changes in clinical practice and use of PRMs).

9.2 Estimated Study Timelines

9.2.1 Part 1

It is estimated that Part 1 will begin at month 1 (February 2014) and will continue over 12 months (February 2014-end January 2015), including both the preparatory work period and the feasibility testing period. It is estimated that the feasibility testing period will commence in September 2014 and will conclude with the analysis of feedback obtained in February 2015.

9.2.2 Part 2

It is estimated that Part 2 will commence in February 2015 (month 13) and will continue over 42 months. Estimated recruitment to the RCT will take place between months 13-35, data collection will take place between months 13-40 and data analysis will take place during months 40-45. The earliest expected enrolment of patients to the post-intervention follow-up component of the trial is month 15. Data collection for this period is estimated to take place between months 15-52, with analysis taking place between months 52-55. The development and testing of the predictive risk models will take place over months 6-46. The evaluation of changes to clinical practice will take place over months 7-44, while the cost-effectiveness evaluation will take place over months 7-51.

Irrespective of trial condition, each patient will be invited to participate throughout active chemotherapy treatment (estimated as 4-6 months for patients completing their chemotherapy treatment without breaches) (up to a maximum of 6 cycles of chemotherapy) and will be followed-up for up to 12 months thereafter. A proportion of patients allocated to explore the clinical utility of the predictive risk models developed; for this sub-group of patients, study participation is expected to be 18-20 months.

A Gantt chart of the timelines for recruitment and data collection is shown in **Figure 6**.

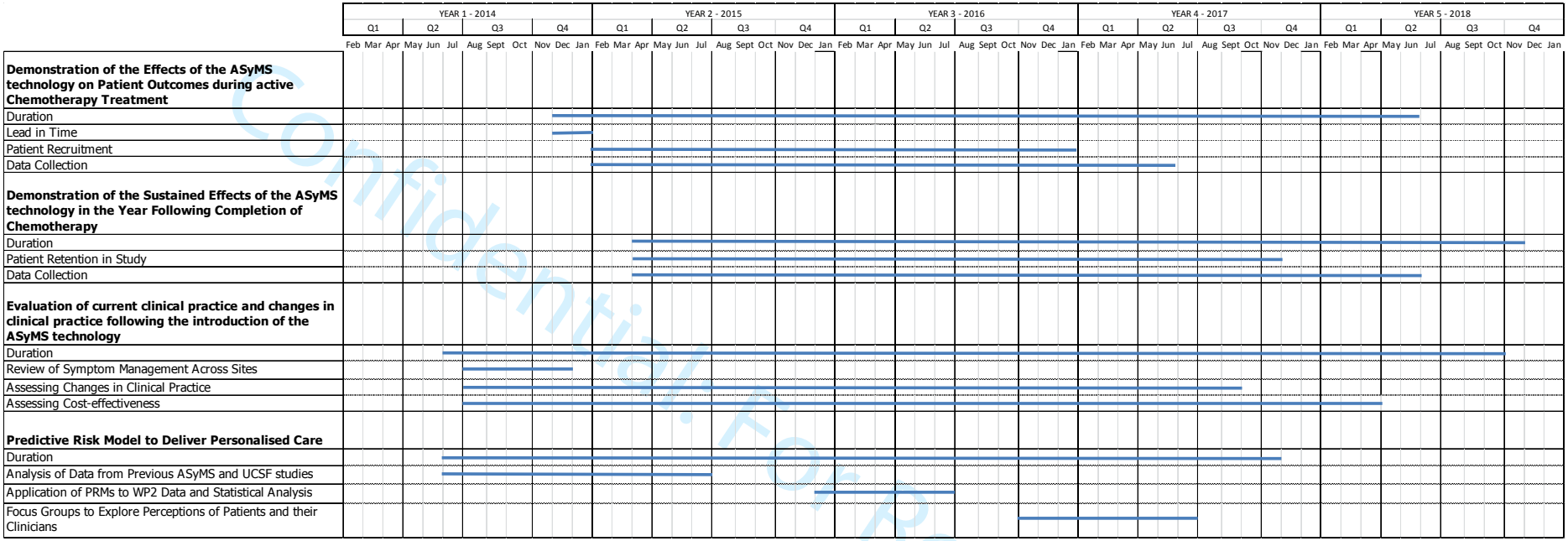

Figure 3. Gantt chart of recruitment and data collection timelines.

10 STUDY CONDITIONS

10.1 Part 1: Feasibility Testing Period

10.1.1 Study Conditions Plan

After a signed informed consent form has been obtained, participants will be asked to use the ASyMS intervention and receive associated training as detailed in Section 9.

10.1.2 Intervention Group

Similar to Part 2; see section 10.2.2 (Intervention Group).

10.2 Part 2: RCT

10.2.1 Study Conditions Plan

After a signed informed consent form has been obtained, participants will be randomly allocated to either use the ASyMS technology (intervention group) or receive standard care (control group). Patient training as detailed in Section 9 will precede actual participation to the study.

10.2.2 Intervention Group

Patients in the intervention group will be instructed to use the ASyMS intervention once daily (and whenever they feel unwell) throughout chemotherapy treatment (maximum 6 cycles). The ASyMS intervention utilises mobile phone technology to enable real-time monitoring of patients' chemotherapy-related symptoms. The core component of the ASyMS intervention is the mobile phone device (i.e. ASyMS patient handset), which contains an electronic version of the ASyMS symptom questionnaire. The ASyMS symptom questionnaire (i.e. CTAQ) assesses ten chemotherapy-related symptoms, namely feeling sick, being sick, diarrhoea, constipation, sore mouth and/or throat, paraesthesia, sore hands and/or feet, flu-like symptoms/infection, tiredness, and pain. An additional item is included to give the patient the option to report up to six additional symptoms that they might experience.

This ePROM evaluates three dimensions of chemotherapy-related toxicity on separate response scales, namely symptom prevalence, symptom severity, and symptom bother. Symptom incidence is reported on a dichotomous scale of yes/no for the eleven items. Where a 'yes' answer is reported, the patient is asked to rate their symptom severity and symptom bother. A 3-point numerical scale (mild, moderate, severe) is used to evaluate symptom severity. The severity indicators have associated descriptors based on the Common Terminology Criteria for Adverse Events (CTCAE V4.0) [48]. Mild symptoms are defined using CTC 1 criteria, moderate symptoms CTC 2 and severe symptoms CTC 3. This ensures that patient ratings of symptom severity are easily translated into routine practice and incorporated into current management guidelines. Finally, a 4-point numerical scale (not at all, a little, quite a bit, very much) evaluates how much a patient is bothered by the symptom. The tenth item relating to pain asks respondents to indicate the location of their pain on a body map. Respondents have the option to report up to 4 different areas of pain. The respondent is also asked if this is a new pain, and to rate the severity and bother of the pain using the same scales as previously described. All items are set to be answered using a recall period of the past 24 hours. The ASyMS symptom questionnaire has been utilised in previous ASyMS studies [15] and validity and reliability of this tool has been demonstrated in people with cancer receiving chemotherapy [15].

Patients will be asked to indicate whether they are at home or in the hospital, complete the ASyMS symptom questionnaire on the ASyMS patient handset, take their temperature through use of a tympanic electronic thermometer, and enter this value into the handset once daily and at any time they feel unwell throughout their chemotherapy treatment. Patients involved in previous ASyMS studies have not found this process burdensome and compliance across patient populations is high [19, 49]. Patients will immediately receive automated, evidence-based self-care advice based on their symptom reports. In addition, patients will also have access to a self-care library, symptom graphs (detailing trends in individual symptoms experienced) and contact numbers of care teams and patient support organisations in their country, available within the ASyMS patient handset.

The patients' 'real-time' symptom information will then be sent automatically via a secured connection to Docobo's (software provider) secure study server. Patients will be advised via the ASyMS patient handset if their symptom data was sent successfully to the study server.

If the patient is hospitalised, their responses will be stored on the study server, but will not trigger any action.

If the patient is at home and the incoming symptom reports are of clinical concern, indicating for example, a developing infection, the software on the server will generate alerts, which will be immediately directed to clinicians at the participating sites.

Two levels of alerts will be generated if symptoms require intervention.

- The first of these, an amber alert (to be addressed within 8 hours), will concern symptoms that are bordering on becoming problematic and would be responsive to early preventative interventions. Following review of the alert, the clinician will have the option to contact the patient (or not). If the clinician takes the decision not to contact the patient on this occasion this will be noted on the system and additional text required to support their decision.
- A red alert (to be addressed within 30 minutes) will be triggered for symptoms that are severe or life-threatening (such as neutropenic events). Following review of the alert the clinician must make contact with the patient.

Both amber and red alerts will be routed to specialist clinicians at the patient's own hospital.

Clinicians will be receiving alerts on a dedicated ASyMS clinician handset, i.e. a mobile phone that the clinician responsible for handling alerts on a given shift ('alert handler') will be carrying with them at all times.

All participating clinical sites will be provided with centrally generated usernames and passwords, specific to each site that will allow clinicians (i.e. alert handlers) access to the ASyMS web-based system. These log-in details will be clinical-site specific, but generic to allow use by any clinician/alert handler. Where clinical site-specific requirements/policies/infrastructure prevent use of generic log-in, an alternative log-in mode will be employed, whereby usernames and passwords will be set as unique for each individual clinician/alert handler. In either case, log-in modes will be employed in accordance to Information Governance policy. Additionally, access to the ASyMS clinician handsets will be facilitated through use of generic log-in details as described above (while handsets will also be protected by a security PIN) or will be password-free, but still protected by a security PIN.

When an alert is triggered, the ASyMS clinician handset will play an audio attention prompt. Alert handlers will be able to identify which patient triggered the alert by tapping the relevant alert icon on the ASyMS clinician handset to reveal the type of the incoming alert (amber or red), the patient study ID number, the time elapsed since the alert was successfully received, and where available, a list of symptoms that triggered the specific alert. This will allow the alert

handler to match the alert to the patient on the secure website, where all patients' symptom reports, demographic and clinical information, contact telephone numbers, and addresses will be viewable.

On receipt of an alert, the clinician will be required to view the patient's 'real-time' symptom reports on a secure web page (ASyMS website), before making a clinical judgement about the most appropriate intervention. Information contained on the secure ASyMS website will include:

- Hospital/identification number
- Name
- Gender
- Age
- Date of birth
- Address
- Contact telephone numbers (3 numbers – study mobile number, own mobile number, landline. Patients will be required to provide 2 out of the 3 phone numbers in light of patient safety)
- Clinical information (cancer type, stage of cancer, details of chemotherapy treatment [drugs, cycle, day] and co-morbidities)
- Details of GP (terminology will be adapted according to each country).

This information will allow clinicians to (a) verify the patient's identity and (b) have the relevant clinical and demographic information at hand to assist in prompt decision making and subsequent intervention. In addition to patient contact details being stored on the ASyMS website for access during alert handling, a hard copy of the patient's study ID number, name and contact details will be kept locked away at the participating site in case the ASyMS server malfunctions or is unavailable. Thus, alert handlers will still be able to contact the patient, if this is deemed clinically necessary, to assess their symptoms and intervene.

Clinicians will be responsible for answering an alert within a set timeframe. Amber alerts will be required to be dealt with within 8 hours, while red alerts will be required to be handled within 30 minutes after the alert has been successfully received by the study server. Clinicians will be able to use information stored on the ASyMS website, i.e. the 28 day view patient display, patient symptom graphs, evidence based self-care advice and a summary report of the patients clinical and demographic information, to conduct a clinical assessment (with the patient if this is deemed clinically necessary). The alert handler will then provide appropriate, standardised interventions, document the actions/interventions performed and finally, sign off the alert on the ASyMS website.

10.2.3 Control group

Patients in the control group will receive standard care as is currently available at their clinical site. Although patients in the control group will not receive the intervention, they will be reminded as per standard practice at the participating hospital sites to make contact with clinicians responsible for their care whenever they wish to discuss any concerns/symptoms they might have during chemotherapy and at follow-up.

10.2.4 Responsibilities

Quality issues should be reported to the Head of Operations and Quality Systems (HOQS) at the Surrey CRC, who will arrange for the most appropriate member of the eSMART technical board to follow up. In the case of complex or delicate quality issues/complaints, an independent person may be appointed by the HOQS. Where appropriate, feedback will be provided to the

eSMART technical board to distribute to all sites to ensure the likelihood of reoccurrence is small.

10.2.5 Compliance

Each participating clinical site will be responsible for performing their own monitoring. The eCRF will enable monitoring that informed consent has been obtained from each participant as well as recording discontinuation/withdrawal from the study and completion. The accuracy and quality of data entered in source documents, the eCRF or ASyMS will be checked with the site research nurse/assistant through reports sent to the Chief Investigator during regular monitoring updates.

See Section 14 for more details on monitoring.

10.2.6 Condition Assignment Procedures

10.2.6.1 Randomisation

Patient randomisation will be performed remotely and independently by the Surrey CRC utilising the PROMSYS system. Research nurses/assistants based at each participating site will log in via a web address to a site from which patients can be randomised 24 hours a day. Eligible patients will be randomised via a web-based eCRF and will be stratified by participating site and type of cancer (breast cancer, colorectal cancer, HD or NHL). It is anticipated that the afore-mentioned steps will ensure that bias in treatment assignment, specifically selection bias, allocation concealment bias and confounding, will be eliminated. At this time, patients who will be taking part in the mid-CTx assessment will also be randomly selected.

Information concerning patient eligibility, patient unique ID number, date of randomisation, allocation group and written informed consent will be recorded within the ASyMS system.

10.2.6.2 Blinding/Unblinding

Due to the nature of the intervention where active patient participation is required, a traditional single-blind (i.e. patient level) or double-blind RCT (i.e. patient and investigator level) is not deemed feasible. However, to mitigate the adverse effects of blinding bias, patient information sheets will be deliberately produced to avoid any reference to 'intervention group' or 'control group' as this could discourage patients allocated to the control group to take part (i.e. they would know that they would not receive the intervention and may withdraw consent). Contrary, all patients will be informed that they will be randomly allocated to one of two 'different methods of symptom management during chemotherapy', i.e. either 'mobile phone group' or 'normal care group'. In addition, participants will be blinded to study hypotheses.

All contact with the patients will be made through research nurses/assistants/designated health professionals (responsible for recruitment, training and data collection) and members of the clinical team (responsible for alert handling and provision of interventions) at each participating site, who however will not be blinded to study condition allocation.

11 EFFECTIVENESS AND SAFETY PARAMETERS

A combination of data collection methods will be employed in the feasibility testing period of Part 1 and in Part 2. Irrespective of study condition, participants will be asked to complete a set of ePROMs at specified intervals throughout their participation in the study (see Section 9). Scores on these ePROMs will act as endpoints to test and confirm/reject the afore-mentioned primary and secondary hypotheses. All participants will have been informed about all procedures involved at the initial consent stage during recruitment.

11.1 Feasibility Parameters (Part 1)

A number of parameters will be evaluated (as outlined in Section 7.2.1 Study Endpoints Part 1), in order to demonstrate the technological readiness of ASyMS at the end of Part 1. A central diary held in each clinical location will be maintained during the feasibility period to record any technological issues reported by patients and clinicians at this time.

11.2 Patient Demographic/Clinical Data (Parts 1 and 2)

An electronic demographic characteristics pro-forma will be completed for each patient by the research assistant/nurse/designated healthcare professional at the start of the study, including variables such as age, gender, marital status, number and age of children, educational attainment, income, ethnicity, lifestyle behaviours (diet, smoking, alcohol consumption, exercise) and current employment type/status. They will also be asked to determine their preferred mode of data collection for post-6 cycles of chemotherapy measurements.

Research nurses/assistants/designated health professionals will be reviewing the patients' medical records (following patient consent) to complete a clinical characteristics pro-forma, including variables such as cancer diagnosis, stage of disease, time since diagnosis, current medications, existing co-morbidities, and chemotherapy regimen. Members of the clinical team will also be asked to assess the patient's performance status through use of the ECOG performance status scale [50].

11.3 ePROMs (Parts 1 and 2)

The outcome measures used in this study have been selected following a review of the literature as advocated by the MRC framework for complex interventions [25-27]. These PROMs coincide with the study hypotheses and have been selected as the best available and most appropriate measures of the outcomes/endpoints identified in Section 6, thus providing evidence to substantiate their use within this project.

11.3.1 Primary Outcome Measure

11.3.1.1 Memorial Symptom Assessment Scale (MSAS)

The MSAS is a multidimensional self-report questionnaire that evaluates 32 physical and psychological symptoms according to their frequency, severity and distress/bother to the person in the past week [51]. This measure has been widely used in the context of cancer care and shown high correlation with HR-QoL and clinical status. Validity of this scale has been widely demonstrated and internal consistency is high with Cronbach's alphas ranging from 0.83 to 0.88 [51]. *Data collection time points:* Baseline and after each CTx (up to a maximum of 6 cycles of chemotherapy); and thereafter 3 monthly for up to a maximum of 12 months. A mid-CTx assessment will take place for a sub-group of patients at each cycle of chemotherapy treatment (up to a maximum of 6 cycles of chemotherapy) (see Section 5.1, Study Flow Chart)

11.3.2 Secondary Outcome Measures

11.3.2.1 Functional Assessment of Cancer Therapy-General (FACT-G)

The FACT-G is a multidimensional self-report questionnaire and consists of 27 items that yield four well-being scales (physical, social/family, emotional, functional) and an overall FACT-G score [52]. It has been widely used with diverse cancer populations and is one of the two most recommended HR-QoL research measures in the field of cancer care. The FACT-G has very well documented psychometric properties including validity, internal consistency, test-retest reliability and responsiveness to change. *Data collection time points*: Baseline and after each CTx (up to a maximum of 6 cycles of chemotherapy); and thereafter 3 monthly for up to a maximum of 12 months (see Section 5.1, Study Flow Chart).

11.3.2.2 Supportive Care Needs Survey-Short Form 34 (SCNS-SF34)

The SCNS-SF34 is a multidimensional self-report questionnaire that evaluates 34 patient needs that fall under the following 5 domains: health system and information; psychological; physical and daily living; patient care and support; and sexuality [53]. SCNS-SF34 has been widely used in cancer research and has very well established reliability and validity. *Data collection time points:* Baseline and after each CTx (up to a maximum of 6 cycles of chemotherapy); and thereafter 3 monthly for up to a maximum of 12 months (see Section 5.1, Study Flow Chart).

11.3.2.3 State-Trait Anxiety Inventory-Revised (STAI-Y)

The Spielberger STAI-Y is a 40-item self-report inventory that assesses the presence and severity of current symptoms of anxiety and a generalized propensity to be anxious [54]. The STAI-Y comprises two subscales, each consisted of 20 items. The State Anxiety Scale (S-Anxiety) evaluates the current state of anxiety ('right now'). The Trait Anxiety Scale (T-Anxiety) evaluates relatively stable aspects of 'anxiety proneness'. The STAI-Y has been used in research involving patients with cancer, where its psychometric appropriateness has been established. *Data collection time points:* Baseline and after each CTx (up to a maximum of 6 cycles of chemotherapy); and thereafter 3 monthly for up to a maximum of 12 months see Section 5.1, Study Flow Chart).

11.3.2.4 Communication and Attitudinal Self-Efficacy scale for cancer (CASE-Cancer)

The CASE-Cancer is a 19-item measure that yields scores on three factors: understanding and participating in care, maintaining a positive attitude, and seeking and obtaining information [55]. It has been used in research with patients with cancer showing high internal consistency and construct validity. *Data collection time points*: Baseline and after each CTx (up to a maximum of 6 cycles of chemotherapy); and thereafter 3 monthly for up to a maximum of 12 months (see Section 5.1, Study Flow Chart).

11.3.2.5 Work Limitations Questionnaire (WLQ)

The WLQ is a 25-item scale that asks respondents to rate their level of difficulty or ability to perform specific job demands [56]. The WLQ's 25 items are aggregated into four scales: time management; physical demands; mental-interpersonal demands; and output demands. The WLQ is easy to use and comprehend, and has shown good psychometric properties in studies with patients with cancer. *Data collection time points*: Baseline and after each CTx (up to a maximum of 6 cycles of chemotherapy); and thereafter 3 monthly for up to a maximum of 12 months (see Section 5.1, Study Flow Chart).

11.3.2.6 EuroQol (EQ-5D)

The EQ-5D is the most widely used with cancer populations and recommended by the National Institute for Clinical Excellence (NICE) in the UK (http://www.euroqol.org/about-eq-5d/how-to-use-eq-5d/who-is-using-eq-5d.html) for its use in cancer research. The EQ-5D comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. It allows calculation of QALYs that are used to inform economic evaluations of health care interventions. Current research supports the validity and reliability of EQ-5D in cancer patient populations. *Data collection time points*: Baseline and after each CTx (up to a maximum of 6 cycles of chemotherapy); and thereafter 3 monthly for up to a maximum of 12 months (see Section 5.1, Study Flow Chart).

11.3.2.7 Client Services Receipt Inventory (CSRI)

The CSRI is a 10 item measure that asks respondents to provide information on the use of services between each interview and includes primary and secondary healthcare contacts, social care, and unpaid care from family members/friends. *Data collection time points*: Baseline and after each CTx (up to a maximum of 6 cycles of chemotherapy); and thereafter 3 monthly for up to a maximum of 12 months (see Section 5.1, Study Flow Chart).

11.4 Assessment of Changes in Clinical Practice (Parts 1 and 2)

In order to determine changes in clinical practice across the participating clinical sites and countries as a result of the application of the ASyMS intervention, a mixed-methods sequential explanatory design will be adopted. The complementary nature of this approach to data collection will ultimately permit understandings and contextualisation of changes in clinical practice by collecting data at baseline and again at the end of Part 2.

Baseline (Part 1):

- Baseline Assessment of Changes in Clinical Practice Questionnaires will be distributed via an online survey tool to data auditors and key clinicians and at each participating clinical site in each country to gather detailed information on current clinical processes and pathways, prior to the introduction of the ASyMS intervention. Questionnaires will focus on a number of central components to establish an understanding of the current organisation of care and current management of chemotherapy related toxicity at each of the participating sites, both during and out with working hours. The questionnaires will also gather specific information on resources used relative to the management of chemotherapy toxicities, such as staff grades, time taken to deal with the toxicities of treatment, healthcare resources used, settings in which care is delivered and patient travel.
- Data from the baseline questionnaires will be pooled for each site in each country to populate a detailed pathway and understanding of the current processes involved in the management of chemotherapy related toxicity, both during and out with working hours for each diagnostic group, as appropriate.

End of Part 2:

- Follow-up Assessment of Changes in Clinical Practice Questionnaires will be distributed via an online survey tool to data auditors and key clinicians and at each participating site in each country to gather detailed information on clinical processes and pathways, post introduction and use of the ASyMS intervention. Similar to the baseline questionnaires, the follow-up questionnaires will focus on a number of central components to establish an understanding of the organisation of care and management of chemotherapy related toxicity at each of the participating sites, both

during and out with working hours, as a consequence of the use of the ASyMS intervention. Again, the questionnaire will gather specific information on resources used relative to the management of chemotherapy toxicities, such as staff grades, time taken to deal with the toxicities of treatment, healthcare resources used, settings in which care is delivered and patient travel.

- The information gathered from the follow-up questionnaires will be used to adapt the pathways of care developed at the baseline stage for each participating site for each participating country, noting changes in processes and current clinical practice as a result of the ASyMS intervention for the management of chemotherapy related toxicity at each of the participating sites, both during and out with working hours.
- To further understand the processes involved in the management of chemotherapy-related toxicity at each of the participating sites, telephone/face-to-face interviews/focus groups with professionals will be undertaken upon collection of quantitative data at the end of Part 2. The telephone/face-to-face interviews/focus groups will verify the identified pathways with those professionals involved in the management of chemotherapy-related toxicity for patients involved in the eSMART study, in both the intervention and control groups. These telephone/face-to-face interviews/focus groups will permit a deeper understanding of current clinical processes and pathways in the management of chemotherapy-related toxicity and gain deeper insights and perspectives of any changes in care as a result of the ASyMS intervention.
- Patients' perspectives of changes in clinical practice will also be explored through the use of interviews (either face-to-face or telephone)/focus groups. Up to 5-10 patients from the Intervention Group per location will be asked, either during or around their completion of the Intervention Phase, to take part in an interview (either face-to-face or telephone)/focus group to explore their experiences of clinical care and technology. A process of maximum variation sampling around age, gender and diagnosis will be used to ensure as representative a sample as possible. Interviews (either face-to-face or telephone) or focus groups will be conducted in the patients' preferred language. An interview schedule, underpinned by a theoretical framework, such as the Technology Acceptance Model, will be developed and used by those responsible for conducting the interviews or focus groups. Interviews/focus groups will be recorded and transcribed (and translated if necessary) for thematic analysis.

The mixed-methods approach adopted is important as it will not only identify possible differences in practices across the sites, but also help understand why these differences have emerged. In addition, the mixed-methods approach will permit a detailed exploration of changes in clinical practice and patient care as a result of the ASyMS intervention and reveal conditions (i.e. conditions not part of the ASyMS intervention) that may have influenced such changes. Finally, the mixed-methods approach will reveal and allow analysis of any common conditions across the sites that are important for practices considered to meet the expectations of improvements of services. Detailed knowledge and understanding of these conditions will be important for the further dissemination of the ASyMS intervention.

11.5 Economic Evaluation of ASyMS (Part 2)

A cost-effectiveness analysis will be conducted from both a health/social care and a societal perspective. The costs of the intervention itself will be calculated by making use of data on ASyMS equipment distributed to patients and staff and patient training required for its use. An element will also be included to cover maintenance of the equipment. It is assumed that these costs at the patient level will be relatively homogenous and so a single intervention cost per month for each country will be used in the analysis, with variations around this used in

sensitivity analyses. Use of other health/social care services during the follow-up period will be measured using an adapted version of the CSRI [57]. Since the mid-1980s, versions of this schedule have been used in around 400 studies internationally. While each version is different, the premise is the same with the aim being to comprehensively record service use associated with an illness over a representative time period. In this study, we will ask participants for retrospective information – covering the periods at baseline, at the end of each CTx (up to a maximum of 6 cycles of chemotherapy), and thereafter 3 monthly for up to a maximum of 12 months – on the use of primary and secondary healthcare services, social care, medication, tests/investigations, and aids and adaptations. The use of unpaid care from family members in specific areas (including personal care, help in and out of the home, childcare, accompanying participant when attending clinic visits etc.) because of the participant's health problems will be recorded as will time taken off work by the participant due to ill health.

The cost of the service use will be calculated by combining the CSRI data with appropriate unit cost information from each country. In the UK, such data are published annually [58]. Some unit cost data will need to be obtained directly from local providers using the costing template document, for example. For other countries we will contact health economic colleagues to compile a list of unit costs similar to those available from the UK. Where costs are not available, we will use a method employed previously whereby UK unit costs are adjusted to reflect differences in healthcare prices between countries [59]. The value of unpaid care and lost employment will be estimated using average wage rates for each country.

Data on the cost-effectiveness of the ASyMS technology will be collected via several sources including the EQ-5D, CSRI, case note reviews, and costing templates. Case note reviews will require access to medical records in order to determine relevant information such as cost due to change in medication, hospitalisation, GP/consultant visits, time spent on the symptom management, social care visits and other health resource use.

The CSRI and the EQ-5D will be completed at baseline, at each CTx (up to a maximum of 6 cycles of chemotherapy) and thereafter at 3 monthly intervals for a maximum of 12 months thereafter. The CSRI, case note reviews and costing templates will collect the following data:

1. Data collected at baseline, at each CTx (up to a maximum of 6 cycles of chemotherapy) and thereafter at 3 monthly intervals up to a maximum of 12 months:
    - Hospitalisation, duration of in-patient treatment
    - Visits to accident and emergency
    - Out-patient/day care appointments
    - GP/consultant/family doctor visits
    - Visits/contacts – community care
    - Visits/contacts – social care
    - Private healthcare costs
    - Medications (prescription and non-prescription drugs) and medical equipment, and changes thereof
    - Time taken off work
    - Time taken off by carers/family to attend appointments
    - Unpaid care provided by family members/friends
    - Time/costs to travel for health/social care appointments.

2. Data collected for treatment period only (up to a maximum of 6 cycles of chemotherapy):
    - Neutropenic events (number and duration)
    - Chemotherapy – Dose reductions/ dose delays/discontinuation of treatment
    - Medications used to manage chemotherapy related toxicity including neutropenia.

The different cost elements will be valued using country specific wages, prices and tariffs collected from manuals, administrative and financial records at each study site.

Clinician costs will also be collected from staff logs/case notes/medical records such as staff time taken to train patients, staff costs in responding to patients, symptom management intervention recorded by staff, and clinician time in dealing with symptoms.

11.6 Development of PRMs (Part 2)

The PRMs will be developed in three distinct parts that will build on each other.

11.6.1 Development of the PRMs Using Existing Data

The first stage of development will use existing data of the research team as well as data generated as part of the eSMART study to develop PRMs for use in patients with breast, colorectal and haematological cancers. Data will be analysed from previous studies [15, 16, 60-64] (see Section 9).

11.6.2 Analysis of Prediction Capabilities

The PRMs developed (from existing data as well as data generated by the eSMART study) will be applied to the data collected from patients participating in the active chemotherapy part of the RCT (*n*=100 patients per cancer type, randomly selected from the total of those recruited) and statistically analysed to assess their prediction capabilities. The variables that will be identified as critical components of the PRMs will be extracted from the data set and sent for analysis. Outcomes to be assessed will include PRM ability to (a) predict an accurate trajectory of each symptom for a given individual; (b) identify symptom clusters; and (c) learn and adapt as new data about an individual is "learnt" as patients progress through their treatment. In addition, the PRMs will be assessed in terms of their capability to predict hospital admissions and neutropenic events. Symptom prevalence, toxicity grading, and symptom clusters will be used to inform these predictions. In addition, the models will be evaluated in terms of their sensitivity and negative and positive predictive values.

11.7 Safety Parameters (Parts 1 and 2)

In the interest of patient safety, patients who will be using the ASyMS technology will be reminded that in cases where a failure in the technology occurs, standard care will apply throughout their participation in the study.

In the interest of patient safety, clinicians will be reminded that in cases where a failure in the technology occurs, standard care will apply for patients in the intervention group throughout their participation in the study.

In addition, all patients will receive contact details in the event of a problem with their participation in the study (detailed within the Patient Information Sheet).

Standard care will apply at all times for patients in Part 2 of the study who are randomly allocated to the control group.

12 SAFETY MONITORING (Parts 1 and 2)

The eSMART Patient Information Sheet will provide all patients with the name, address, and telephone number of a contact person at the participating site for information in the event of a problem with their participation in the study. The Patient Information Sheet will advise patients to keep this information safe and accessible should they need it at any time during their participation in the study.

12.1 ASyMS handset Software: Device Classification and CE Rationale

12.1.1 Classification

The software running on the ASyMS handset has been classified as a **Medical Device** based on the following underlined text taken from the Medical Devices Directive EEC 93/42:
'medical device' means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment Or alleviation of disease,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;

The software running on the ASyMS handset is considered a non-invasive device, given that according to the MEDICAL DEVICES: Guidance document – Classification of medical devices (http://ec.europa.eu/health/medical-devices/files/meddev/2_4_1_rev_9_classification_en.pdf), an invasive device is "a device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body." Based on **Figure 7** taken from the Medical Devices Directive EEC 93/42 Annex IX and the following statement (http://ec.europa.eu/health/medical-devices/files/meddev/2_4_1_rev_9_classification_en.pdf):

Non-invasive Devices
All non-invasive Devices are in class I, unless one of the rules set out hereinafter applies.

Because no other rules apply except for Rule 1, the ASyMS handset is therefore a Class I device.

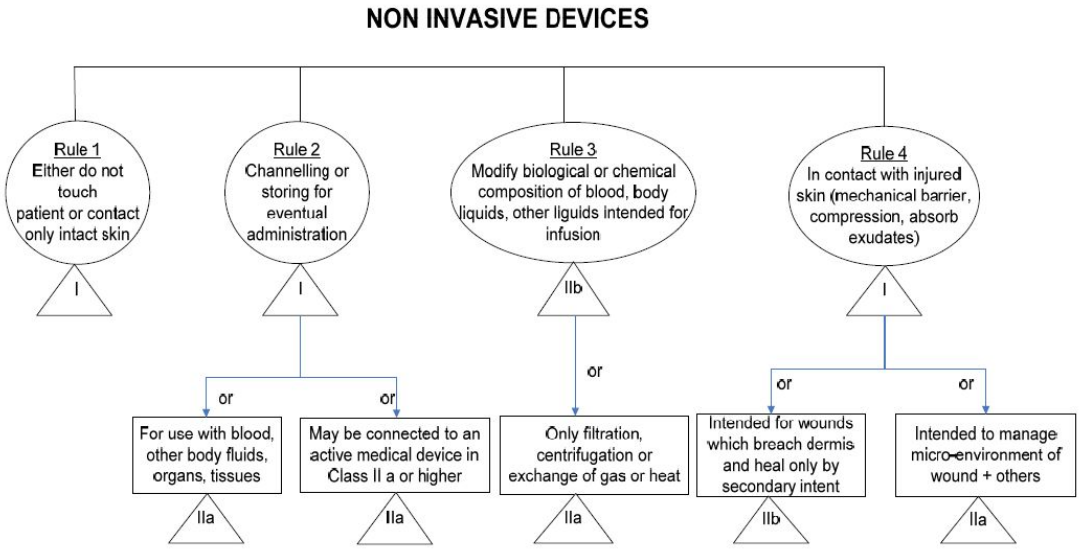

Figure 4. Graphical summary of a medical devices classification guidance chart for initial identification of probable device class – Non-invasive devices (From: http://ec.europa.eu/health/medical-devices/files/meddev/2_4_1_rev_9_classification_en.pdf).

12.1.2 CE Rationale

According to the MEDICAL DEVICES: Guidance document – Classification of medical devices (http://ec.europa.eu/health/medical-devices/files/meddev/2_4_1_rev_9_classification_en.pdf), "irrespective of the class of the device, all devices must:

- meet the essential requirements, including the requirements regarding the information to be supplied by the manufacturer (Annex I of the Directive 93/42/EEC);
- be subject to the reporting requirements under the medical device vigilance system;
- be CE marked."

As CE devices, the software running on the ASyMS handsets will be used in line with their intended purpose and in accordance with the essential requirements; therefore, the proposed RCT is not considered to be a medical device trial. According to the Medical Devices Directive EEC 93/42, *"Intended purpose" means the use for which the device is intended according to the data supplied by the manufacturer on the labelling, in the instructions and/or in promotional materials.*

12.2 Specification of Safety Parameters

12.2.1 Definition of an Incident

Any event which meets all three basic reporting criteria **A-C** listed below is considered as an INCIDENT and must be reported to the relevant National Competent Authority (Information on incidents occurring following placing of devices on the market. MEDDEV 2.12-1 rev 6, December 2009; http://ec.europa.eu/health/medical-devices/files/meddev/2_12_1-rev_6-12-2009_en.pdf). The criteria are that:

A: An event has occurred

This also includes situations where testing performed on the device, examination of the information supplied with the device or any scientific information indicates some factor that could lead or has led to an event.
Typical events may include, but are not limited to:

a) A malfunction or deterioration in the characteristics or performance. A malfunction or deterioration should be understood as a failure of a device to perform in accordance with its INTENDED PURPOSE when used in accordance with the MANUFACTURER's instructions.
b) False positive or false negative results falling outside the declared performance of the device.
c) Unanticipated adverse reaction or unanticipated side effect
d) Interactions with other substances or products
e) Degradation/destruction of the device (e.g. fire)
f) Inappropriate therapy
g) An inaccuracy in the labelling, instructions for use and/or promotional materials. Inaccuracies include omissions and deficiencies. Omissions do not include the absence of information that should generally be known by the intended USERs.

B: The MANUFACTURER's device is suspected to be a contributory cause of the INCIDENT
In assessing the link between the device and the INCIDENT the MANUFACTURER should take account of:

- the opinion, based on available evidence, of healthcare professionals;
- the results of the MANUFACTURER's own preliminary assessment of the INCIDENT;
- evidence of previous, similar INCIDENTs;
- other evidence held by the MANUFACTURER.

This judgement may be difficult when there are multiple devices and drugs involved. In complex situations, it should be assumed that the device may have caused or contributed to the INCIDENT and the MANUFACTURERs should err on the side of caution.

C: The event led, or might have led, to one of the following outcomes:

- death of a patient, USER or other person
- serious deterioration in state of health of a patient, USER or other person

NOTE: Not all INCIDENTs lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of healthcare personnel.
It is sufficient that:

- an INCIDENT associated with a device happened, and
- the INCIDENT was such that, if it occurred again, it might lead to death or serious deterioration in health.

12.3 Evaluating, Recording and Reporting Incidents

The investigator or designee is responsible for detecting, documenting and reporting incidents. These must be recorded in the source incident form and/or eCRF.

For all incidents, the following must be assessed and recorded on the relevant documentation:

a) Date of Report
b) Date of Incident
c) Description of incident
d) Action taken with regard to participation in the study.

The following authorities should be notified in the case of an incident:

- The National (local) Competent Authority. This includes the following National Competent Authorities:
  - Austria: Austrian Agency for Health and Food Safety (http://www.ages.at/).
  - Greece: National Organization for Medicines (http://www.eof.gr/).
  - Ireland: Health Products Regulatory Authority (http://www.hpra.ie/).
  - Norway: Norwegian Medicines Agency (http://www.legemiddelverket.no/).
  - UK: Medicines and Healthcare products Regulatory Agency (devices) (http://www.mhra.gov.uk/).

- The local REC that has reviewed the initial ethics application for this study at the country where the clinical site is based (reporting to be customised according to local policy).

The following process will be followed to notify the above-mentioned authorities on any incidents:

1. The clinical site will report the incident to the Chief Investigator.
2. The Chief Investigator will notify the NCA and/or the software developer company (i.e. Docobo Ltd.) about the specific incident(s).
3. Once evaluated by the NCA/Docobo Ltd., the NCA/manufacturer will issue a Field Safety notice (FSN) if required.
4. If a FSN is issued in any country, then the Chief Investigator will obtain a copy of the FSN from the NCA/Docobo Ltd.
5. The Chief Investigator will submit all reported FSNs to the main REC in the annual report and to the DMC.
6. The Chief Investigator, where applicable, will notify all sites of FSNs

13 ANALYTICAL PLAN

13.1 Responsibility for Analysis

A separate document, the Statistical Analysis Plan (SAP), will be developed by the trial statistician in discussion with the investigators and finalised prior to datalock. This will be signed off by the chief investigator, trial sponsor and statistician. The SAP will contain in detail the information outlined below.

13.1.1 Part 1: Preparatory Work

The analysis of the data obtained from the preparatory work of Part 1 will be the responsibility of University College Dublin and University of Strathclyde.

13.1.2 Part 1: Feasibility Testing Period

The analysis of the data obtained from the preparatory work of Part 1 will be the responsibility of University College Dublin and University of Strathclyde.

13.1.3 Part 2: RCT

The statistical analysis of the data obtained from this study will be the responsibility of the Surrey CRC in conjunction with University of Dundee.

13.2 Data Analysis

13.2.1 Part 1: Preparatory Work

Information received from the participating sites will be tabulated and reviewed to reveal technological requirements at each site.

Findings from the systematic review of local and international guidelines and recommendations on symptom management will be incorporated in a narrative analysis.

13.2.2 Part 1: Feasibility Testing Period

All feedback will be descriptively and content analysed, and any emerging issues will be addressed prior to Part 2.

13.2.3 Part 2: RCT

13.2.3.1 Subject disposition

The number of subjects completing each assessment visit, together with a summary of the number of days between visits, will be tabulated. The number of subjects withdrawn during the course of the study will be tabulated by reason for withdrawal.

13.2.3.2 Population description

Demographic and clinical characteristics recorded at screening will be tabulated by treatment sequence for both the efficacy and safety populations. Descriptive statistics will include n, mean, standard deviation, median, minimum and maximum.

13.2.3.3 Effectiveness Analysis

All analyses will follow the guidance contained in the ICH E9 'Statistical Principles for Clinical Trials' (http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928.pdf). Analysis of this RCT data will be based on the intention-to-treat principle.

All subjects, who meet the inclusion/exclusion criteria and have provided at least one wave of data, will be included in the analysis of the effectiveness parameters.

13.2.3.3.1 Intervention Phase (up to a maximum of 6 cycles of chemotherapy)

Study outcomes will be described as means and standard deviations. Transformations may be required where the distributions are clearly non-normal. Baseline characteristics will also be described for the whole trial and separately by type of cancer in the three groups. The primary outcome of MSAS is continuous and will be assessed in a repeated-measures analysis utilising mixed models. Hence, the analysis will test the difference between ASyMS and standard care in the change in symptoms between baseline and repeated follow-up at the end of each chemotherapy treatment. The primary hypothesis will be tested through the regression parameter for arm of the study (ASyMS v. Standard Care), adjusting for baseline MSAS as well as stratified by type of cancer (breast, colorectal, haematological) and country. Adjustment will also be made for length of treatment, age, gender, symptom prevalence at baseline and severity at baseline. The pre-specified subgroup analyses by type of cancer, country, age, gender, symptom prevalence and severity will be assessed by fitting trial arm by subgroup interaction parameters. The extent of missing data in the outcomes will be explored and the reasons for missingness noted. If necessary, multiple imputation will be used to impute missing values assuming data is MAR. The use of mixed models has the advantage that with MAR, all data is utilised in the analysis.

Should the active recruitment period of the RCT over run, it is acknowledged that this may affect the number of patients with data at all time-points at the designated end of the follow-up period (also end of Part 2). During the follow-up period, a separate analysis will be performed to indicate how many patients would be required by the end of month 52 (i.e. end of follow-up period).

13.2.3.3.2 Follow Up Phase (following a maximum of 6 cycles of chemotherapy)

Two mixed-models analyses will be carried out. Firstly, the repeated measures of outcomes in the extended follow-up will be added to those already obtained from the active chemotherapy period. This will essentially be a longer-term follow-up of the active chemotherapy period and has the advantage of further repeated measures adding power to the comparison. It will also test whether any effect seen after the trial is sustained for up to a year. Post-chemotherapy treatment management is highly individualised, therefore groups of patients are expected to receive different maintenance treatment based on cancer diagnosis and disease characteristics and different models of follow-up (traditional, open access, versus risk stratified) and therefore additional sub-group analyses will be performed and adjustment made for these differing characteristics in the modelling.

Secondly, a separate analysis will take baseline as the end of chemotherapy and analyse the repeated measures of the outcomes up to 12 months. This will be an observational cohort analysis of the post-intervention stage and will therefore require more confounding factors to be taken into account. The analyses will utilise mixed models as in the active chemotherapy period. The extent of missing data in the outcomes will be explored and the reasons for missing data noted.

Data analysis will need to be modified to account for the mixed mode design for collecting follow-up data. The primary outcome analysis will ignore mechanism of collection. However, the mixed mode of collecting follow-up data will need to be taken account of during secondary data analysis. Secondary analysis will allow the mechanism of data collection – via tablet; internet survey, or telephone – to be assessed in the regression model of the primary outcome. This will determine whether outcome varies significantly by mode of collection. If it does, results will be presented separately by individual method of collection (in effect a subgroup analysis).

13.2.3.4 Subgroup Analyses

Any subgroup analyses will be performed by type of cancer, gender, site at least facilitated by adding intervention by subgroup interaction terms into the regression model. Such analyses would be secondary and generating hypotheses. Where important differences are found results would then be presented separately by subgroup.

13.2.3.5 Deviations from the statistical plan

Any deviation(s) from this plan will be described and justified in a protocol amendment and/ or in the final statistical report, as appropriate.

13.2.4 Part 2: Assessment of Changes in Clinical Practice

Data gathered from the Assessment of Changes in Clinical Practice Questionnaires (baseline and follow-up) will be pooled for each site within each country for each separate time point in the first instance. Data will also be pooled across all countries where possible. Descriptive statistics (i.e. univariate analyses) will be used to present quantitative descriptions of this data by clinical site in a manageable form. In addition, to compare the data for each site, and potentially across all the sites, at the baseline and follow-up periods, inferential statistics (e.g. paired t-tests, McNemar tests) will be conducted on the data to compare for any changes that might be evident as a result of the use of the ASyMS technology.

Any free text/qualitative text captured within the Assessment of Changes in Clinical Practice Questionnaires (both baseline and follow-up) will be pooled for each site in each country and across all countries where possible and analysed thematically, at the within and between case level.

13.2.5 Part 2: Cost-Effectiveness Analysis

13.2.5.1 Cost analyses

Costs will be compared between both arms of the study for the period between baseline and each follow-up period. This analysis will use a regression model controlling for baseline costs and country. Cost data usually follow a skewed distribution and this may result in similarly skewed regression residuals. If this is the case we will use non-parametric bootstrap methods to generate confidence intervals around the cost difference estimates.

13.2.5.2 Cost-effectiveness analyses

Data will be analysed in Stata. Cost comparisons between the groups will be made at each follow-up using a regression model. The dependent variable will be the cumulative cost up to that time point and the group identifier will be the independent variable. If the regression residuals are clearly non-normally distributed, we will use non-parametric bootstrapping to generate confidence intervals around the coefficient representing cost differences. If the economic evaluation finds that using ASyMS costs less and is more effective (produces more

QALYs), then this will indicate 'dominance'. If the intervention costs more and is more effective an incremental cost per QALY will be calculated. This will give information on how much more the invention costs to generate an extra QALY. In both these cases there will be variation around the cost and QALY estimates and so we will generate cost-effectiveness planes using non-parametric bootstrapping and cost-effectiveness acceptability curves using the net benefit approach. These will in turn show: (i) the probability that the intervention is cost decreasing and outcome improving, cost decreasing and outcome reducing, cost increasing and outcome improving, or cost increasing and outcome reducing and (ii) the probability that the intervention is cost-effective for different values placed on a QALY.

Sensitivity analysis will also be conducted to assess the robustness of the results.

13.2.6 Part 2: Telephone/face-to-face interviews/focus Groups

Telephone/face-to-face interviews/focus groups with patients, clinicians and professionals will be audio recorded and transcribed verbatim. All non-English transcripts will be translated into English before data analysis commences. Themed categories will be identified by two researchers based on the research objectives and questions. Analysis of the data will be thematic but focused on whether and how participants agreed or disagreed about each issue. Thematic content analysis [69] is a useful approach for answering questions about the salient issues for a particular group of respondents or for identifying typical responses. For reliability and validity purposes, two researchers will code interviews separately and then cross-check them together.

13.2.7 Part 2: Predictive Risk Modelling

Data from previous ASyMS and UCSF studies as well as data generated from the eSMART study will be analysed and used to develop initial PRMs. Two sets of PRMs will be developed: one set derived using standard mathematical modelling (utilising techniques such as logistical regression, latent growth curve analysis, hierarchical linear modelling (HLM), reasoned modelling, Bayesian inference and curve fitting) and the other developed using machine learning (including neural networks and evolutionary algorithms). The sets of models will then be combined, resulting in 3 hybrid PRMs, one each for use in modelling symptoms in people with breast, colorectal and haematological cancers, respectively.

The PRMs developed will be applied to the data collected from patients participating in the active chemotherapy part of the RCT (n=100 patients per cancer type) and statistically analysed to assess their prediction capabilities. Two-sided t-tests will be used to measure the correlation between symptoms. The AUROC test will be used to measure predictive capability of the models. It is also important to assess the calibration of the models and this will be performed by applying the Hosmer-Lemeshow test.

13.3 Justification of Sample Size

13.3.1 Part 1: Feasibility Testing

A maximum of 6 patients per participating site will be screened and invited to take part in the feasibility testing period. This sample size is deemed adequate for the exploratory nature of this component [65].

In addition, $n \leq 20$ clinicians at each site will be asked to take part in an assessment of changes in clinical practice questionnaire prior to full deployment of the ASyMS intervention. This sample size is deemed adequate for the purposes of this component.

13.3.2 Part 2: RCT

Sample size estimation for this RCT was based on existing evidence on differences in total MSAS scores (i.e. primary outcome measure) between intervention group (1.45) and control group (1.30), i.e. a difference between intervention and control groups of 1.45-1.30=0.15 [66]. Drawing on this data, a sample size estimation analysis indicated that for a difference in total MSAS score of 0.15 (SD=0.6) given an effect size of 0.25, with 4 repeated measures after baseline and one baseline measure, a sample of 776 patients will provide 90% power for a 2-sided 5% significance level [67]. Allowing for an attrition rate of 30%, a total of 1108 patients will need to be recruited.

During the follow-up period, it is assumed that a further 30% of participants will dropout, thus giving a sample of 544 expected to complete the study 12 months follow-up.

In addition, to allow for a mid-CTx comparison of MSAS scores between intervention and control group, a random 30% of the total sample recruited for the RCT, i.e. *n*=334 [*n*=122 patients with colorectal cancer (61 intervention/61 control), *n*=122 patients with breast cancer (61 intervention/61 control), and *n*=90 patients with haematological cancer (45 intervention/45 control)] will be selected to provide data at this time-point.

13.3.3 Part 2: Post-RCT

13.3.3.1 Telephone/face-to-face interviews/focus groups interviews about changes in clinical practice

Up to *n*=10 members of the local clinical team and between 5-10 patients who received a mobile phone at each participating site in each country will be invited to participate in telephone/face-to-face interviews/focus groups following the introduction and use of the ASyMS intervention to gain perspectives of any changes in care. Group sizes typically range from five to eight, but no larger than ten participants, for focus groups of this nature [68]. Groups larger than 10 participants are not only difficult to control, but they can also limit each person's opportunity to share their observations, experiences and insights [68].

13.3.3.2 Focus groups/interviews regarding use of PRMs

Two focus groups/interviews per participating site will be held with patients (*n*=1) and members of the local clinical team (*n*=1) to explore the perceived utility of the PRMs in clinical practice and in their ability to provide relevant information to inform the delivery of a preventative and anticipatory model of care. Up to *n*=10 patients and *n*=10 clinicians will be invited. Group sizes typically range from five to eight, but no larger than ten participants, for focus groups of this nature [68]. Groups larger than 10 participants are not only difficult to control, but they can also limit each person's opportunity to share their observations, experiences and insights [68].

13.4 Anticipated Response Rates (Parts 1 and 2)

Response rates in previous ASyMS studies [15, 17, 18] and symptom modelling studies [16] and partner studies [60-64] ranged from 62%-90%, and based on the number of patients receiving chemotherapy for the first time in 2012 across all the study sites, the anticipated rates of accrual will be achievable for the requirements of this part. In addition, the spread of patients across all study sites, incorporating a range of demographic and treatment characteristics, demonstrates that the results obtained from eSMART will be applicable to the wider population of patients receiving chemotherapy.

13.5 Level of Significance (Part 2)

All tests will be conducted with a 2-tailed level of significance of 0.05.

13.6 Procedures for Handling Missing, Spurious or Unused Data (Part 2)

13.6.1 Part 1: Feasibility Testing Period

Although no specific procedures for handling missing data will be followed in this period, the extent of missing data will be established to inform the approach to be pursued in Part 2.

13.6.2 Part 2: RCT

Initially the pattern of missing data will be assessed and the extent of missingness will be determined. All efforts will be made to minimise missing data, especially in the primary outcome. Where missing data occur for a data set being analysed, the resultant data set will be analysed as unbalanced without imputation being employed, the SAS procedure that will be used, MIXED, being able to carry out maximum likelihood estimation taking full account of the available data, provided missing data are missing at random (MAR). The mechanism by which data have become missing will be recorded and a judgment made whether this is consistent with the assumption of MAR. All missing, spurious, or unused data will be listed by subject.

13.7 Definition of Study Completion (Part 2)

Study completion is defined as the date the last patient participates in the post-trial assessments in Part 2.

13.8 Definition of Criteria for Termination of the Study (Part 2)

Study termination is defined as a permanent discontinuation of the study due to unanticipated concerns of safety to the study subjects or availability of other new data.

13.9 Data processing and statistical analysis

The data processing and statistical analysis of the results will be performed by the trial statistician with support from Surrey CRC in conformity with Surrey CRC procedures.

The statistical analysis will be conducted using SAS® (SAS Institute, NC, USA) and Stata (StataCorp, TX, USA).

The qualitative analysis will be facilitated by QSR NVivo©.

14 STUDY DOCUMENTATION ADMINISTRATION

14.1 RCT Registration

The RCT will be registered in *clinicaltrials.gov* (https://clinicaltrials.gov/), a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

14.2 Source documents and CRF/eCRF

The object of eSMART is to use as many electronic methods as possible. The source should always be the first place that the data is recorded.

Data entered into the ASyMS system both by the patients and site clinical staff and the ePROMS on the tablet will be considered as source data. Demographic information will need to be entered into the Randomisation system to allow randomisation and this will be classed as source.

Information for this study will be collected from a variety of sources, including patient case notes. In this case, data from patient case notes will be extracted and stored in the eCRF and ASyMS system and this will be considered source.

Other data may be collected from a number of different sources, for example to provide the financial information to analysis the cost benefit. It may not be possible to list all the difference sources across the different countries. However if major discrepancies in data are seen from one or two specific sites, they may be requested to provide further information on where the data was gathered.

All forms should be filled out using a black ball-point pen, and must be legible. All entries, corrections and alterations are to be made by the responsible investigator or her/his designee. With the exception of obvious mistakes, the corrections need to be commented. Corrections should be made in such a way that the original entry is not obscured. The corrected data should be entered, dated, and initialled by the investigator or his designee.

Notes taken at meetings will be considered source and it will be the responsibility of the researcher to provide these notes in a Word or similar document as close as possible to the notes taken whilst allowing for the need to make them as clear as possible to other researchers.

Audio recordings from focus groups and interviews will be considered source and it will be the responsibility of the researcher to transcribe as accurately as possible.

The investigator at each site is responsible for the validity of the data collected at that site.

14.3 Clinical Site Monitoring

Data will be evaluated for compliance with the protocol and accuracy in relation to source documents.

Surrey CRC will develop a monitoring plan which will record all of the information regarding monitoring, but each participating clinical site will be responsible for performing their own monitoring.

The accuracy and quality of data entered in source documents, the eCRF or ASyMS will be checked with the site research nurse/assistant through reports sent to Surrey CRC and the Chief Investigator during regular monitoring updates to ensure:

- The safety and rights of patients are respected (good information given to patients, informed consent form signed and dated correctly, confidentiality of data, no wrong inclusion, good care and follow-up during their participation in the trial)
- Proper maintenance of all trial documentation
- Smooth day-to-day running of the trial

All documents generated by the clinical sites which form part of this trial, and the ensuing data, must be made directly available so that data can be verified.

The Chief Investigator agrees to allow audits of the trial sites and of all trial documentation by the Sponsor or its representatives.

14.4 Access to Source Data Documents

The investigator will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data/documents.

The monitors and researchers will have access to records.

14.5 Data Handling and Record Retention

Docobo (study software providers) will be responsible for retaining anonymised and non-anonymised data from this study for a minimum of 5 years after the study end and must obtain the permission of the eSMART coordinator or delegate if they wish to delete or archive data. Retention of data will be subject to Docobo standard Information Governance safeguards in accordance with the requirements of ISO 27001 and those of the NHS Information Governance Toolkit (controlled access, safe storage, assurance of integrity, management of risks associated with loss of data and breach of confidentiality).

In order to comply with new EU regulation 2016/679 and its associated EU directive 2016/680 (publish April 2016, compliance mandatory from 6 May 2018), provision has been made for the confidential information held by Docobo on study subjects and clinicians involved in the study, to be removed within 20 days of a request for such removal having been issued by that person. Furthermore, in order to comply with another aspect of the new regulation and new directive, provision has been made for one of these persons to be provided with the detailed data held on them within 20 days of making such a request.

Surrey CRC will be responsible for retaining the anonymised data from this study for a minimum of 10 years after the study's end according to University of Strathclyde policy and must obtain the permission of the eSMART coordinator or delegate if they wish to delete or archive data. The procedures that will be followed for the collection, storage, protection, retention and destruction of all information comply with national and EU legislation.

The investigator must maintain adequate records to enable the conduct of the study to be fully documented. The investigator should arrange for retention of the essential documents in the investigator's Trial Master File for at least 10 years after the end of the study. No study-related documents will be destroyed until receipt of written permission from the Sponsor.

Any difficulty in storing original documents should be discussed with the monitor prior to initiation of the study.

14.6 Technical Support Procedures

All technical support procedures detailed hereafter are applicable to the active chemotherapy period of the RCT. In general, if the signal on the ASyMS patient handset is poor and therefore transmission of an ASyMS symptom questionnaire is not feasible at the time of its completion, then data will be stored on the handset and transmitted the next time that there is a connection, i.e. the next time they are in an area with a good mobile phone signal. Patients will be immediately informed of a failure to transmit information. They will immediately be advised to contact their clinical site using a landline to notify them of any urgent symptoms or symptoms that are becoming worse. Should any of the signs or symptoms be of concern, the clinician will initiate interventions as appropriate following local guidance/clinical protocols.

14.6.1 Technical Support

Clinicians involved in this study will attend a training course on the ASyMS intervention, during which they will be informed of all procedures to deal with any problems, should they occur. Patients and clinicians will be provided with a manual on how to use the phone and solutions to common problems that they may encounter when using the ASyMS handset. If the patient experiences any difficulties that cannot be rectified using the manual provided, they will be advised to contact their clinical site. The clinician will then try to 'troubleshoot' the problem with the patient using the instruction manual provided. If this proves to be unsuccessful on this occasion, the clinician will elect to use the web based support system which is available 24 hours a day, seven days a week. If the problem cannot be rectified with technical help, the patient will be sent a new ASyMS patient handset via courier. The same procedure will apply for the tympanic digital thermometer. Each clinical site will have a supply of spare handsets and tympanic thermometers for dispatch on such occasions. In the interim (which is anticipated to be no more than 48 hours), prior to receiving their new ASyMS patient handset, patients will be advised to follow standard care as outlined by their local clinical site.

14.6.2 Clinical support

Clinical support will be provided 24 hours-a-day, seven days a week as per standard care by the clinical site. To ensure patient safety, patients who will be using the ASyMS intervention will be reminded that in cases where a failure in the technology occurs, standard care will apply throughout their participation in the study. Also, clinicians will be reminded that in cases where a failure in the technology occurs, standard care will apply for patients in the intervention group throughout their participation in the study. All patients will receive contact details in the event of an emergency.

14.6.3 Quality assurance

Members of the local clinical teams responding to patient alerts will be required to record all interactions and interventions within the secure ASyMS website from drop down menus/open text boxes.

14.7 Subject Confidentiality and Data Protection

The ASyMS intervention meets the standards laid down in the Data Protection Act and the Health and Social Care Information Centre (http://systems.hscic.gov.uk/). There are strict

protocols for the management of confidential patient information. The processes that will be monitored by the Caldicott Guardian or similar entity in the partner countries where this applies:

- All patient identifiable information that will be used only for their care.
- Summary reports and Management information will use only non-patient identifiable information.
- All information will be transmitted to and from the patient in an encrypted format.
- All data held on the web database will be held securely with secure usernames and passwords and access will be given only to the research team, and the patients' clinical team with signed consent from the patient.

All research data recorded throughout this study will be regarded as confidential. Patient contact details will used by the research nurses/assistants/designated health professional at the participating sites to contact participants to confirm participation in the study, reconfirm participation during the study, and to send short update reports on the progress of the project and to clinical staff responding to alerts. Members of the local clinical teams will use patients' contact details that are stored on the ASyMS system itself to deal with incoming patient alerts. Patients' contact details will be stored separately and securely in a locked cabinet and they will be destroyed following 6 to 12 months after the last contact, according to University of Strathclyde policy.

Participants will be provided with guarantees of confidentiality and anonymity in the storage, analysis and reporting of the study. All electronically collected data will be stored in a 'safe haven' server environment hosted by Docobo (software company partner) to maintain the security of patient identifiable data. The procedures that will be implemented for data collection, storage, protection, retention and destruction of data and the technical and process orientated measures to be employed by Docobo all comply with national and EU legislation. This includes complying with Article 29 (Data Protection Working Party paper WP131) on the processing of personal data relating to health in electronic health records. A range of IT best practice measures, that are compliant with the requirements of ISO 27001, will be employed to mitigate against unauthorised access to any data within the safe haven. The consortium will incorporate any revisions detailed in the revised Directive 95/46/EC on Data Protection and Privacy. The Surrey CRC will be responsible for ensuring that any revisions to the directive are incorporated into data protection and privacy for eSMART.

Interview/focus group transcripts will be stored on password-protected computerised files. For the purposes of transcription and subsequent data analyses, encrypted password-protected data sticks will be used and will be transferred from clinical sites to translation and/or transcription services via recorded delivery services. Hard copy transcripts will be stored in locked filing cabinets in a central location (School of Health Sciences) and will be accessed only for translation purposes and/or data analysis by members of the research team and/or by authorised analysts.

All research data collected will be stored securely in a separate locked cabinet at School of Health Sciences, and will only be available to members of the eSMART research team and data analysts, who will need access for data analysis purposes. All data will be transferred to electronic password-protected databases, which again will be accessed by the eSMART research team for data collection and analysis purposes. Following the completion of data collection, all demographic, clinical data and completed questionnaires will be archived and stored securely for a minimum of 10 years, according to University of Strathclyde policy.

No identifiable information will be associated to any of the data generated from the study. No patient will be asked to fill out their name on any questionnaire. A unique eSMART identification number will be matched to respondents' actual name and this will be used throughout their participation in the study. These ID numbers will have already been applied to the ePROMs completed by the study participants on the PC tablets. All data generated through completion of ePROMs and use of the ASyMS patient handset will be transmitted to a secure GCP-compliant database located at the eSMART office with a copy on the database maintained at the Surrey

CRC, University of Surrey. Participants will have been informed prior to actual consent of this intention, but it will be re-confirmed with them that their ID number will in no way be associated to their name.

If queries are posed by the participants about their responses to the ePROMs items, the research nurse/assistant will provide explanations in such a manner that prevents manipulation of the patients' responses. Finally, participants will be assured that any conversations held during the telephone/face-to-face interviews/focus groups will remain confidential between the participant and the researchers.

14.8 Arrangements for Individuals with Special Communication Needs

Although all of the study documentation will have been translated in three languages, translated versions will be relevant to context and country only. The same will apply to the original English versions. While it is acknowledged that cultural diversity within each country exists, eligibility of patients in this study will be dependent on their satisfactory ability to speak, read, write and understand the respective language. This is to reduce complexity in the collection and analysis of data, as well as in the associated costs.

14.9 Arrangements for Individuals who Lose Capacity to Consent during the Trial

Should a participant, who has given informed consent to the trial, lose capacity to re-confirm consent during the study, the participant will be withdrawn from the study. No further clinical or non-clinical interventions or procedures will be carried out on the participant under the study protocol. No new personal data will be collected. No further data would be collected as intact capacity is required for completion of questionnaires. Subject to ethical approval, data already collected in relation to the participant may be retained and used for the purposes for which consent will have already been given, provided they are effectively anonymised and no longer identifiable to the research team or any other persons to whom access will be given.

14.10 Arrangements for Future Research Work involving Patient Data Collected during the Study

Two occasions have been identified, where patient data collected during eSMART may be required for/used in future research work:

- Use of data in secondary analyses. In order to be able to use data from eSMART for secondary data analysis for purposes out with the aims and objectives of eSMART, all patients will be asked to provide written consent to grant permission for their data to be used in secondary analyses, while treating data with strict confidentiality.
- Use of personal data to contact patients for future work. In order to be able to access patient personal data to invite them to take part in future work (e.g. involving long-term follow-up), all patients will be asked to provide written consent to grant permission for their personal data to be accessed and used to (a) check the patient's health status with their hospital and/or GP/oncology consultant/family physician, and (b) contact patients, while treating this data with strict confidentiality.

15 QUALITY CONTROL AND QUALITY ASSURANCE

The site must not randomise any patients until the Sponsor and Health Authorities approvals are in place. The Sponsor approval is dependent on receipt of approval from the main REC, and site specific approvals.

It will be the responsibility of the site PI to ensure the accuracy of all data entered at his/her site. They must conduct the trial personally, or delegate to members of their research team specific tasks using a delegation log. They must ensure that each member of their research team is suitably qualified to perform delegated tasks by education, training and experience, and must ensure that written procedures are followed to enable the collection of high quality data.

Research nurses/assistants/designated health professionals will inform the Sponsor of any protocol deviations that impact on patient safety or validity of the data. The Chief Investigator will report to the REC any breaches or deviations that are, in his/her opinion, of major significance. Minor breaches and deviations will be summarised in the annual reports and circulated to the REC.

Within 90 days after the end of the trial, defined as the final visit of the last patient, the Sponsor will ensure that the REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be issued within 15 days after the termination date which is defined as the final patient visit. The Data Monitoring Committee (DMC) will also be informed.

The Sponsor will supply a Clinical Study Report of the clinical trial to the REC within one year after the end of the trial. The report will also be communicated to the DMC.

16 CLINICAL TRIAL PROTOCOL DEVIATIONS AND AMENDMENTS

Any 'substantial' protocol amendment(s) (meaning that it could have a significant impact on the safety or physical or mental integrity of the patients, the scientific value of the trial, or the conduct or management of the trial) must be submitted to the Independent Ethics Committee (IEC) and the NHS R&D office (or similar in the partner countries) prior to its implementation.

For non-substantial changes that do not affect the safety or validity, e.g. an administrative change, the EU Directive does not require the IEC to be notified. However, for Surrey CRC, the amendment will be forwarded to the IEC for their information, and the changes implemented immediately, unless otherwise instructed by the sponsor or IEC.

In the case of changes consisting of urgent safety measures to protect the trial subjects, the sponsor should inform the IEC as soon as possible after these measures have been implemented.

In the case of any non-substantial protocol amendments, it *may* be necessary to notify all sites. This will be decided on a case by case basis. In the case of any substantial protocol amendments, it *will* be necessary to notify all sites.

17 CONDITIONS FOR TERMINATING THE STUDY

Study completion is defined as the date the last patient participates in the post-trial assessments in Part 2.

Study termination is defined as a permanent end of the study due to unanticipated concerns of safety to the study subjects or availability of other new data.

If, in the opinion of the Chief Investigator, there are incidents in the study that suggest that it may be unwise to continue, the investigator may terminate part of, or the entire study, after consultation with the sponsor, or the sponsor may terminate part of, or the entire study, for safety or administrative reasons. A written statement fully documenting the reasons for such termination will be provided to the IEC.

18 ETHICAL AND REGULATORY REQUIREMENTS

The study will be conducted in accordance with:

- The protocol,
- The UK Data Protection Act, 1998, and
- The guiding principles of the Declaration of Helsinki.

18.1 Informed Consent

It is the responsibility of the local site PI and research nurse/assistant to obtain written informed consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. This includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any study specific procedures. Participants will be given written information outlining the study details given approval by the IEC. Any changes to the approved version of the information sheet/consent form must be approved by the IEC prior to its implementation, unless it is for urgent safety measures. A copy of the signed consent form will need to be given to the participant.

The local site PI and research nurse/assistant must also explain that the participant is completely free to refuse to enter the study or to withdraw from it at any time. The eCRF for this study contains a section for documenting date of informed consent, and the local site PI and research nurse/assistant must complete it appropriately.

18.2 Independent Ethics Committee (IEC)

This protocol and any accompanying material provided to the participants (such as the information sheet or description of the study used to obtain informed consent) will be submitted by the Chief Investigator, or person under her responsibility, to the appropriate IEC. Approval from the committee must be obtained in writing before starting the study and the approval letter must reference which documents were reviewed and approved.

Any required changes will be forwarded to the IEC for their approval. Written approval of the revised documents should also be obtained from the IEC. Depending upon the exact changes, written approval of the revised documents may not be required prior to the commencement of the screening process.

The IEC must provide a copy of their membership list, and a list of names of those members present at the meeting when the study was reviewed. The IEC must also have provided a copy of their constitution, and a signed statement indicating that it complies with GCP, that will be kept on file at Surrey CRC.

18.3 Annual/Final Reports

In accordance with GCP regulations, the Chief Investigator will notify the IEC within 90 days of the end of the study. If the study is terminated prematurely, this reporting timeframe will be reduced to 15 days from the termination of the study.

The study report will be provided to the IEC within one year of completion of the study, as defined in Section 18 of this protocol.

The Sponsor will be responsible for submitting annual reports to the IEC.

19 FINANCE AND INSURANCE

Prior to starting the study, the Sponsor will secure funding for the conduct of this study, and will enter into a Clinical Trial Agreement with the funder. Each of these agreements will include the financial information agreed upon by the parties.

Reimbursement, indemnity and insurance shall also be addressed in the Clinical Trial Agreement.

20 PUBLICATIONS AND DISSEMINATION

In collaboration with ECPC, the dissemination, communication and exploitation of results will be publicised using different modes, including publications in scientific journals; establishment of an eSMART website with publicly accessible general information for the public; and production of a toolkit for implementing/utilising the ASyMS technology in a variety of clinical practice areas and other transferable health care contexts.

Dissemination of research results will be undertaken by the consortium. All partners, in particular the academic and R&D institutions, have excellent track records in scientific publications, conference presentations and engagement with public fora.

All the results, including, research, state of the art and market analysis will be disseminated first among the partners of the consortium and then to the scientific community, via scientific journals, conferences, symposia, seminars, trade exhibitions, public engagement events, scientific festivals, host institutions web sites and press releases. This all-encompassing dissemination strategy will demonstrate the expertise of the consortium and the results of the trial and related work packages.

The dissemination of the results from the eSMART project will have two main strands.

Strand one will be the dissemination of information about the trial and related work packages to the lay public. This will mean that the results and the demonstration of the use of EU funding will reach as wide an audience as possible. ECPC will be the central organising body for this dissemination strand. This will involve dissemination through ECPC's extensive network of 300 organisations for patients with cancer in over 45 countries via multiple media including their website and other publications. In addition, ECPC will play a lead role in the organisation of dedicated symposia for patient groups and the end of project conference.

Strand two will focus on the dissemination of information about the trial to the scientific community. This will demonstrate best practice and distribute the results and study design, allowing other researchers to replicate these in other contexts.

The dissemination, communication and exploitation of results will be publicised using different media appropriate to the different target audiences:

- Publications in field-specific scientific journals and, if applicable, in broad-subject journals (for information to the scientists, researchers, business).
- Attendance at appropriate conferences, such as European Cancer Organisation (ECCO), American Society of Clinical Oncology conference (ASCO), Multinational Association of Supportive Care in Cancer (MASCC), to establish contacts and exchange information with scientists and practitioners in relevant fields.
- Establishment of an eSMART website with publicly accessible general information for the public as well as a section on publications and scientific progress.
- Organisation of a results conference in Brussels for specialists outside the consortium towards the end of the project.
- Organisation of training workshops and events for consortium researchers and staff of eSMART partner organisations to transfer and embed the knowledge and expertise generated by the project.
- Participation in workshops and scientific events in the areas of interest of this trial organised by other consortium groups.
- Produce a toolkit on implementing/utilising ASyMS in a variety of clinical practice areas and other transferable health care contexts.

20.1 General public

eSMART, in conjunction with ECPC, will use the following tools to disseminate information about the trial to the general public.

20.1.1 eSMART website

A public website will be created to present the main goals and expected benefits from eSMART, in conjunction with ECPC, in terms of:

- Positioning the research project in EU Research (in the area of clinical trials).
- Providing information for non-specialists on how research spending at European level in specific areas of clinical trials can reduce symptom burden and improve patient experience of potentially distressing symptoms associated with chemotherapy treatment.
- Publication in lay terms of scientific and technical achievements.

20.1.2 Press releases

When appropriate, usually at the launch and completion of the project and when research results are available, the eSMART team, in conjunction with the host University press office, will prepare press releases, ensuring efficient publicising of the results. In addition, summaries of research results will be posted on the website and, in keeping with international copyright laws, linked to an abstract or the full text of the peer-reviewed article.

20.1.3 Open access publication

Several journals now provide open access to published papers. eSMART project partners will publish research results in open access journals providing maximum accessibility of the scientific results. The costs of open access publications have been included in the budget.

20.2 Scientific community

20.2.1 Scientific publications and presentations

As the eSMART consortium has as its main activity Research and Technological Development (RTD), the primary method of dissemination will be through publication in high impact scientific journals. All academic partners have a proven publication history in high impact scientific journals. There is an increasing demand for an interdisciplinary approach to publication in high impact journals. The complementary expertise of the consortium, therefore, is in an ideal position to meet this expectation.

20.2.2 Participation in conferences workshops and seminars

Research results will be presented at scientific meetings by each of the project members. In addition, all of the partners in eSMART already have expertise in speaking at invited seminars and international conferences. When presenting at international events, funding by the EC will be clearly highlighted.

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22 APPENDIX

Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

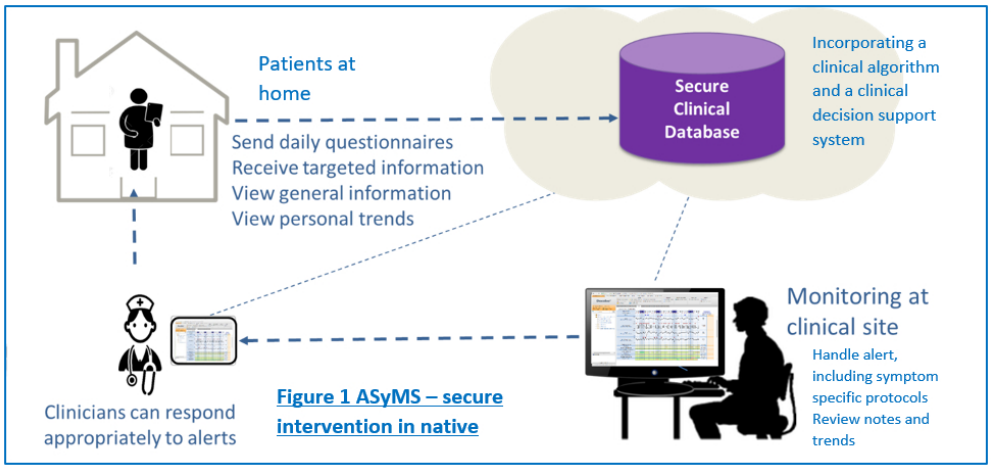
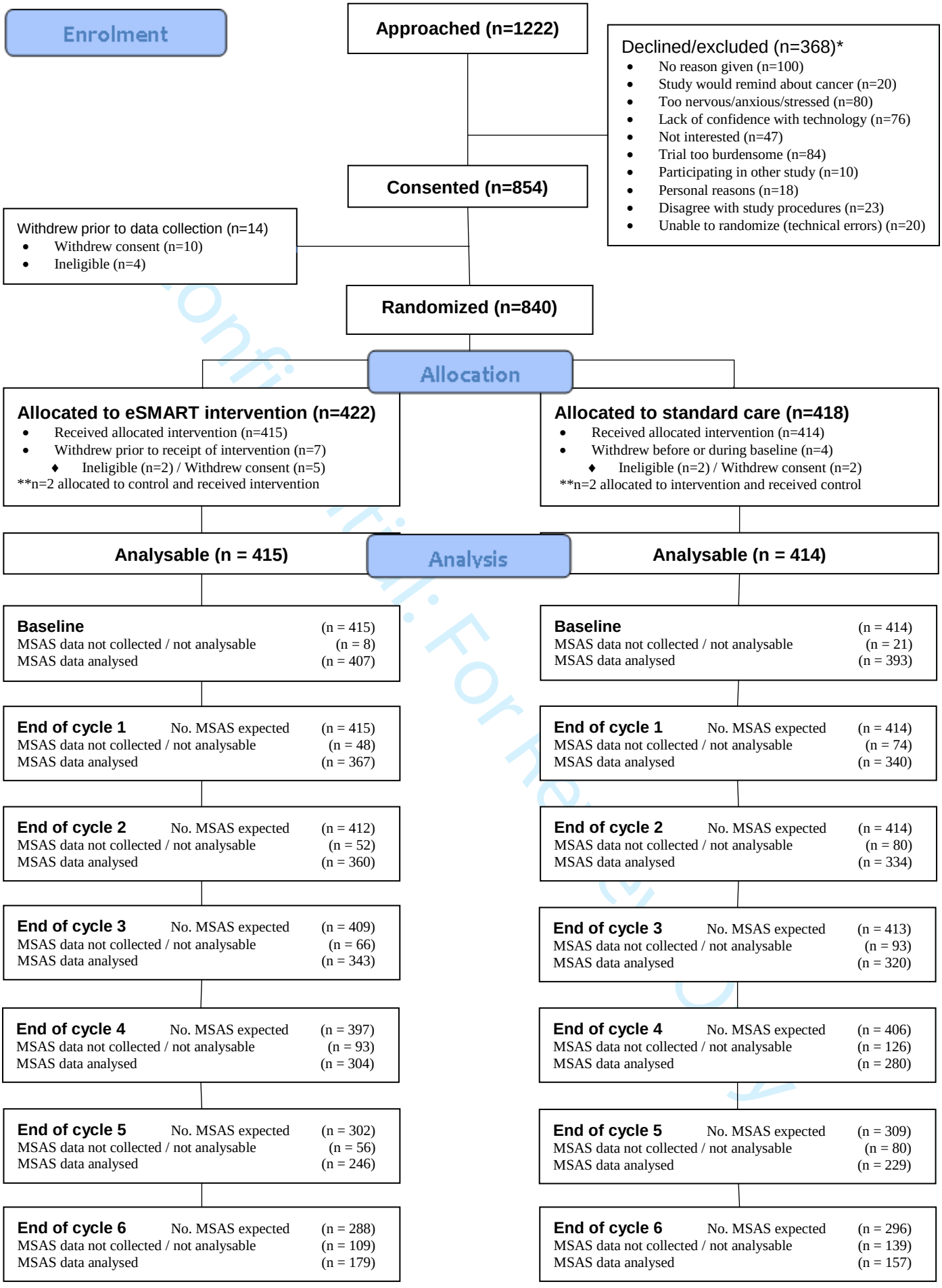


Figure 1 ASyMS – secure intervention in native



*Note: Some people reported more than one reason for not wanting to take part therefore the total number of reasons exceeds the number declined/excluded

Figure 2. CONSORT diagram eSMART

Overview of the Nausea and Vomiting Symptom Management Protocols on ASyMS