APPENDIX 1: eSMART Sponsor and Clinical sites

Sponsor Representative	Dr Sophie Wehrens **Address:** Research Enterprise Support, Level 4, Senate House, University of Surrey, Guildford, Surrey, GU2 7XH
Participating Site #1	**Site Name:** Medical University Vienna Comprehensive Cancer Center, **Name of Principal Investigator (PI) or Clinical Team Representative:** Professor Dr Alexander Gaiger, M.D. **Address:** Medical University Vienna Comprehensive Cancer Center, Spitalgasse 23, BT86/E 01, A-1090 Wien, Austria
Participating Site #2	**Site Name:** Agioi Anargiri Cancer Hospital, **Name of Principal Investigator (PI) or Clinical Team Representative:** Miss Anna Papadouri, RN, MSc **Address:** Timiou Stavrou, Kifisia, 145 64, Athens, Greece
Participating Site #3	**Site Name:** Metropolitan Private Hospital **Name of Principal Investigator (PI) or Clinical Team Representative:** Dr Vasilieos Barmpounis, **Address:** 9 Ethnarxou Makariou & 1 El.Venizelou, 18547, Neo Faliro, Athens, Greece
Participating Site #4	**Site Name:** Air Force General Hospital, **Name of Principal Investigator (PI) or Clinical Team Representative:** Dr Chrysoula Karlou RN, MSc, PhD, Head Nurse **Address:** Panagioti Kanellopoulou 3, 115 25, Athens, Greece
Participating Site #5	**Site Name:** St James's Hospital, **Name of Principal Investigator (PI) or Clinical Team Representative:** Professor John Kennedy **Address:** St James's Hospital, P.O. Box 580, James's St, Dublin 8, Ireland
Participating Site #6	**Site Name:** St Vincent's University Hospital, **Name of Principal Investigator (PI) or Clinical Team Representative:** Dr Giuseppe Gullo **Address:** Elm Park, Dublin 4, Ireland.
Participating Site #7	**Site Name:** St Vincent's Private Hospital, **Name of Principal Investigator (PI) or Clinical Team Representative:** Dr Giuseppe Gullo **Address:** Herbert Avenue, Dublin 4
Participating Site #8	**Site Name:** Innlandet Hospital Trust, Divisjon Lillehammer, **Name of Principal Investigator (PI) or Clinical Team Representative:** Dr Geir V. Berg **Address:** Sykehuset Innlandet divisjon Lillehammer, Postboks 104, 2381 Brumunddal, Norway
Participating Site #9	**Site Name:** Guy's and St Thomas' NHS Foundation Trust, **Name of Principal Investigator (PI) or Clinical Team Representative:** Michael Flynn, Chemotherapy Nurse Consultant **Address:** Guy's and St Thomas' NHS Foundation Trust, 4th Floor Bermondsey Wing, Guy's Hospital, Great Maze Pond, London, SE1 9RT, UK
Participating Site #10	**Site Name:** Mount Vernon Cancer Centre, Middlesex, UK **Name of Principal Investigator (PI) or Clinical Team Representative:** Ms Teresa Young

	Address: Mount Vernon Cancer Centre, Mount Vernon Hospital, Rickmansworth Rd, Northwood, Middlesex, HA6 2RN, UK
Participating Site #11	**Site Name:** St George's Healthcare Trust, **Name of Principal Investigator (PI) or Clinical Team Representative:** Dr Ruth Petteng **Address:** St George's Healthcare NHS Trust, Blackshaw Road, Tooting, London, SW17 0QT, UK

Insert hospital/ site logo

APPENDIX 2: Participant Consent Form

eSMART STUDY (PART 2): PARTICIPANT CONSENT FORM – Patient
Version 4; 11/07/2016

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

Name of Principal Investigator: *Local Site Clinical Lead/Hospital Consultant*

Please initial the box next to each statement if you agree, or place a cross in the box if you do not agree.

1. I confirm that I have read and understood the Information Sheet [*date and version to be inserted*] for the above study. I have had the opportunity to consider the information and ask questions, and have had these questions answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that if I am allocated to the mobile phone group in this study taking part involves completing a daily symptom questionnaire for up to 6 cycles of chemotherapy (which takes about 5 minutes a day). ☐
4. I understand that, regardless of what group I am allocated to, taking part in this study involves completing 8 questionnaires at the start of my treatment and at the end of each cycle of chemotherapy (up to a maximum of 6 cycles). This will takes between 40-60 minutes. ☐
5. I understand that relevant sections of my medical notes and data collected during the study may be looked at by appropriate individuals from the hospital, the University of Surrey, from regulatory bodies or from the organisation co-ordinating the study, where it is relevant to my taking part in this research. Data collected during the study may be looked at by responsible representatives from the sponsor (University of Surrey) for the purposes of monitoring and auditing to ensure that the study is being conducted properly. I give permission for these individuals to access my records and data. ☐
6. I understand that my hospital number [*equivalent term to be substituted in each country as appropriate*] and other data about me (as outlined in the Information Sheet) will be held electronically on a computer system. I also understand that my eSMART study identification number, name and details regarding my chemotherapy regime will be stored on the study mobile phone to ensure I get asked the right questions in the questionnaire. I give permission for my data to be stored in this way. ☐
7. I agree that the information that I provide in the questionnaires can be used anonymously in future studies for the purposes of secondary data analysis. ☐
8. I agree for my anonymised responses to the Work Limitations Questionnaire to be shared with the questionnaire's developer (i.e. Tufts Medical Centre, USA). ☐

9. I agree to my GP [*equivalent term to be substituted*] being informed of my participation in the study. ☐
10. I agree to my GP [*equivalent term to be substituted*] being contacted by the research nurse/assistant/designated health professional to ask about my health status before the research nurse/assistant/designated health professional contacts me for any of the study assessments that take place at 3, 6, 9 and 12 months after I have participated in the study for a maximum of 6 cycles of chemotherapy. ☐
11. I agree that the research nurse/assistant/designated health professional can contact members of my clinical team if I become distressed during the study. ☐
12. I agree that I may be contacted in the future by researchers involved in this study who would like to invite me to participate in follow-up studies to this project, or in future studies of a similar nature. I give permission to researchers involved in this study to contact my hospital and/or GP/oncology consultant/family doctor [*equivalent to be substituted*] to ask about my health status before contacting me. ☐
13. I agree to take part in the above study. ☐

NAME OF PARTICIPANT	**DATE**	**SIGNATURE**
_____	_____	_____

NAME OF RESEARCHER OBTAINING CONSENT	**DATE**	**SIGNATURE**
_____	_____	_____

1 original for participant, 1 original to be kept in medical notes and 1 copy for study file.

Insert hospital/ site logo

APPENDIX 3: Participant Information Sheet

Version 5; 01/08/16

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

Invitation

You are being invited to participate in the above research study. Before you decide, it is important for you to understand why this research is being done and what it will involve. Take time to read the following information carefully and discuss it with others if you so wish. Please contact us if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

Chemotherapy is a common treatment for people with cancer. It can be associated with a number of side effects and symptoms, which if not adequately managed can have a negative impact on the lives of people living with cancer. Chemotherapy is often delivered on an outpatient basis and most people have to manage the side effects of their treatment at home, with limited input from health professionals. Therefore, it is important to look at ways of supporting people receiving chemotherapy to manage their symptoms during periods when they are at home. We are conducting a large study called eSMART to evaluate the impact of mobile phones in the management of symptoms and side effects of people with Breast or Colorectal or Haematological Cancer (Hodgkin Disease or non-Hodgkin Lymphoma) during their chemotherapy and for one year following completion of their treatment. The study is being conducted in two parts.

You are being asked to participate in **Part 2** of the study **only**. The aim of Part 2 is to determine whether the use of the mobile phone system is better or worse than current care in the reporting and management of chemotherapy related symptoms during treatment and for one year following treatment. Part 2 is expected to last for 40 months in total; however, you will only be involved for approximately 18 months. This is split over your chemotherapy treatment (a total of 4-6 months depending on the duration of your chemotherapy treatment, you will only participate in this Part of the study for up to a maximum of 6 cycles of chemotherapy) and the first 12 months after this.

Why have I been invited to participate?

A member of your clinical care team has approached and invited you to participate because you are due to receive chemotherapy for a diagnosis of Breast, Colorectal or Haematological Cancer (Hodgkin Disease or non-Hodgkin Lymphoma). A total of 1,108 patients from different hospitals within a number of European countries will participate in this study.

Do I have to participate?

No. It is your decision whether or not you wish to participate. If you do decide to take part, you will be given this Participant Information Sheet to keep and you will be asked to sign a Consent Form. You

are free to withdraw from the study at any time, which will in no way affect the standard care you receive. However, any study data that you will have provided up until withdrawal may be retained and used for analysis purposes.

What will happen if I take part?

In this study, patients will be randomly allocated into two groups. One group will report their symptoms using a mobile phone, whilst the other group will receive care that is normally provided at their hospital. Patients will participate in the study for up to a maximum of 6 cycles of chemotherapy and then for one year following this.

The groups that patients will be allocated into will be selected by a computer, which has no information about the individual, so people will be selected by chance. Patients in both groups will have their symptoms and other outcomes (including quality of life, supportive care needs, work limitations, confidence in ability to complete tasks and anxiety) compared. Details of the two groups are given below:

Mobile phone group

If you are allocated to the 'mobile phone' group, you will be given a mobile phone and an ear thermometer for taking your temperature. A health professional involved in your chemotherapy treatment or a researcher/research nurse working on this study will show you how to use both the phone and the thermometer. A booklet for the mobile phone containing instructions and helpful contact numbers will also be supplied.

During your chemotherapy treatment (up to 6 cycles), you will be asked to complete a short symptom questionnaire on the mobile phone once a day and anytime you feel unwell. This questionnaire will ask you whether or not you are in hospital and questions about symptoms you may experience at this time. Every time you complete the questionnaire, you will be asked to record your temperature on the thermometer provided and enter your temperature recording on the mobile phone. It is estimated that each time you complete the questionnaire and take your temperature will take you no longer than 5 minutes.

This symptom information will then be sent to a computer system which will analyse your symptom reports and trigger an alert to healthcare professionals at your hospital if you experience moderate or severe symptoms. Reporting your symptoms using the symptom questionnaire on your mobile phone will trigger the following actions:

- If you are experiencing ***moderate symptoms***, an amber alert will be sent to health professionals at your hospital to inform them that you are experiencing symptoms that may require some advice and/or treatment. For an amber alert, a health professional will review your symptom report within **8** hours of receiving it and, depending on your symptoms, may decide to call you at home to offer you advice.
- If you report ***severe symptoms***, a red alert will be sent to healthcare professionals at your hospital and they will call you **within 30 minutes** from the time that you completed and sent your symptom questionnaire to discuss your symptoms and offer advice/treatment as appropriate.

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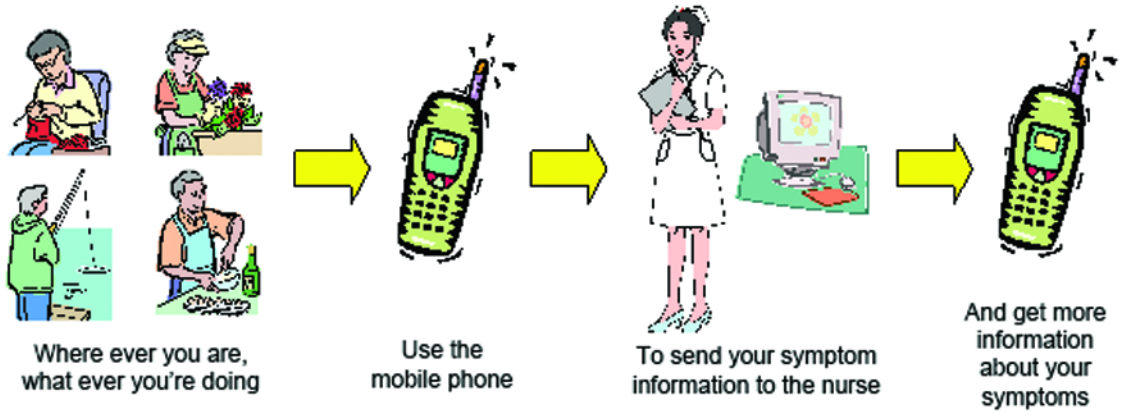
If you answer that you are 'in hospital' on your mobile phone, your symptom information will be sent to the study server, however **no alerts** will be sent to your health professionals.

You will also receive **self-care advice** on the mobile phone on how to manage any symptoms you may be experiencing. You will be able to view graphs of your symptoms on your mobile phone at any time. In addition, your doctor or nurse will have the option to print off graphs of your symptom reports that may be included in your hospital notes for review by your clinical team. If you experience any problems with the mobile phone system, you will be advised to follow the standard procedures for reporting symptoms/problems at your clinical site. You will be asked to inform health professionals at your hospital about any problems with the mobile phone system that you may be experiencing. You will also be supplied with a booklet for the mobile phone containing instructions and helpful contact numbers.



At the beginning of your chemotherapy treatment and before the start of each subsequent chemotherapy cycle (up to 6 cycles) you will also be asked to complete a set of eight questionnaires on a computer tablet or PC. Completing these questionnaires should take between 40 to 60 minutes of your time. These questionnaires will explore issues regarding your quality of life, confidence in ability to complete tasks, anxiety, work-related issues, use of health care services and any other symptoms you are experiencing.

A sub-set of patients (30% of the total patient sample) will also be randomly selected and asked to complete a symptom questionnaire midway through each chemotherapy cycle (up to a 6 cycles). If you are selected for this assessment, a research assistant/nurse/designated health professional participating in the study will call you via telephone at this time and ask you to provide answers to the symptom questionnaire over the phone. You will not be provided with any advice on how to manage your symptoms during this call.

At the end of your 6th cycle of chemotherapy treatment (or earlier if you finish your chemotherapy before this), you will be asked to return the mobile phone and the thermometer provided to you at the start of the study. If you continue to receive chemotherapy treatment after you have returned the mobile phone, you should follow the normal standard care procedures of your clinical site.

Finally, following completion of your 6th cycle of chemotherapy treatment (or earlier if you finish your chemotherapy before this), you will be asked to complete the same set of questionnaires within a week of finishing chemotherapy and 3, 6, 9 and 12 months later. With your permission, before

contacting you on any of these occasions, the researcher/research nurse working on this study will first contact your GP/oncology consultant/family doctor [*equivalent to be substituted*] to check with him/her your health status so that the researcher/research nurse does not disturb you if you feel too unwell to take part. On any of these occasions, you will be offered the option to complete the questionnaires either in person at your hospital using a tablet computer, PC or via the internet at home or via telephone at home.

Normal care group

If you are allocated to the 'normal care' group, you will report your symptoms according to normal local practice as employed by your hospital.

At the beginning of your chemotherapy treatment and before the start of each subsequent chemotherapy cycle (up to 6 cycles) you will also be asked to complete a set of eight questionnaires on a computer tablet or PC. Completing these questionnaires should take between 40 to 60 minutes of your time. These questionnaires will explore issues regarding your quality of life, confidence in ability to complete tasks, anxiety, work-related issues, use of health care services and any other symptoms you are experiencing.

A sub-set of patients (30% of the total patient sample) will also be randomly selected and asked to complete a symptom questionnaire midway through each chemotherapy cycle (up to 6 cycles). If you are selected for this assessment, a research assistant/nurse/designated health professional participating in the study will call you via telephone at this time and ask you to provide answers to the symptom questionnaire over the phone. You will not be provided with any advice on how to manage your symptoms during this call.

Following completion of your 6th cycle of chemotherapy treatment (or earlier if you finish your chemotherapy before this), you will be asked to complete the same set of questionnaires within a week of finishing chemotherapy and 3, 6, 9 and 12 months later. With your permission, before contacting you on any of these occasions, the researcher/research nurse working on this study will first contact your GP/oncology consultant/family doctor [*equivalent to be substituted*] to check with him/her your health status so that the researcher/research nurse does not disturb you if you feel too unwell to take part. On any of these occasions, you will be offered the option to complete the questionnaires either in person at your hospital using a tablet computer, PC or via the internet at home or via telephone at home.

What is the procedure being tested?

Overall, the study is testing the impact of a mobile phone system to manage the symptoms and side effects of people with Breast, Colorectal, or Haematological cancer (Hodgkin Disease and non-Hodgkin Lymphoma) during their chemotherapy and for one year after the end of it.

What are the side-effects or disadvantages of taking part in the study?

As this study does not affect the treatment and care that you are receiving, there are no real side-effects of taking part. However, if you are allocated to the 'mobile phone' group, as you will be completing a daily symptom questionnaire you may be thinking about your symptoms more than you might if you were not asked to complete the questionnaire. Some people may find it upsetting to focus

on their symptoms, whilst others find this helpful or do not notice any difference. If you did feel that taking part in the study was making you think too much about your symptoms, then you can withdraw from the study without having any effect on your future treatment and care. You should discuss these feelings or concerns with your doctor or nurse. [*Local contact details will be inserted here*].

In addition, you might find completing the study questionnaires a burden. You will be given adequate time to complete the questionnaires at your own pace, and a research assistant/nurse will always be available should you need any help. However, if you find completing these questionnaires overly tiring or frustrating, then you can withdraw from the study without this having any effect on your future treatment and care.

What are the possible benefits of taking part?
If you are allocated to the 'mobile phone' group, the possible benefits of participating are that during periods after chemotherapy, whilst you are at home, the symptoms that you may experience will be remotely monitored and health professionals will be alerted if you are experiencing moderate or severe symptoms that require treatment and/or advice. Furthermore, each time you enter your symptoms on the mobile phone, you will receive self-care advice linked to the symptoms that you are experiencing, which may assist you to manage your symptoms at home. In addition, on the mobile phone there is a library of helpful information for people undergoing chemotherapy such as advice on feelings and emotions and living with and beyond cancer. You will also have a list of important contacts on your mobile phone, such as numbers of care teams and patient support organisations available in your country. Finally, your nurse will have the option to print your reported symptoms from the computer and file these in your hospital notes. This may help you to remember and discuss the symptoms you experienced at home for when you visit your doctor or nurse at the hospital.

If you are allocated to the 'normal care' group, you may not experience any direct benefits of participating in this study. However, the information and feedback you provide may be beneficial for other patients with cancer in the future as it will help us to understand the impact of the mobile phone system as we will compare the symptoms and the information from people in the 'mobile phone' group and the 'normal care' group.

What if new information becomes available?
Sometimes during the course of a research project new information can becomes available regarding the procedures being tested. If this happens, your doctor or nurse will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your doctor or nurse will make arrangements for your treatment and care to continue, and it will not be affected in any way. If you decide to continue in the study you might be asked to sign an updated consent form. Also, on receiving new information, your doctor or nurse may consider it to be in your best interests to withdraw you from the study. They will explain the reasons and arrange for your treatment and care to continue. However, any study data that you will have provided up until withdrawal may be retained and used for analysis purposes.

What happens when the research study stops?
Your participation in the study will continue until 12 months after either the end of your chemotherapy treatment (if it is fewer than 6 cycles), or up to 6 cycles of chemotherapy. If you received a mobile phone and thermometer to report your symptoms, you will be asked to hand this back following the

completion of your chemotherapy treatment (or up to a maximum of 6 cycles of chemotherapy). At the end of the study, you will receive standard care as is normal at your hospital.

What if you have questions or if something goes wrong?
If you have any comments or complaints about this study, or should you need to get in touch with your clinical site in the event of a problem with your participation in the study, you should contact your doctor or nurse (see contact details below). *Please keep these contact details safe and accessible at all times should you need them.*

Name and contact address/details (including telephone number) of Doctor and Nurse to be inserted.

If you do not get a satisfactory response from them, you are free to contact the sponsor of this study at the address below.

Name and contact address/details (including telephone number) of Sponsor to be inserted.

If you believe that you have been harmed in anyway by taking part in this study, you have the right to pursue a complaint and seek any resulting compensation through the University of Surrey which is acting as the research sponsor. Details about this are available from the research team. Also, as a patient of the NHS, you have the right to pursue a complaint through the usual NHS process. Note that the NHS has no legal liability for non-negligent harm. However, if you are harmed and this is due to someone's negligence, you may have grounds for a legal action against NHS but you may have to pay your legal costs.

Will my participation in this project be kept confidential?
All information that is collected about you during this study will be kept strictly confidential. If you decide to take part and are allocated to the mobile phone group, information about you will be stored securely on the study server and will be treated as strictly confidential. This information includes your hospital/identification number, name, gender, age, date of birth, address, contact telephone numbers and clinical information, i.e. details of your diagnosis and treatment/other medical conditions that you have. Storing this information on the study server is appropriate to cross-check your information with your nurse if they need to contact you and to assist in clinical decision making.

In addition, your name, your study identification number and details of your chemotherapy regime will be stored on your mobile phone. This is to ensure you get asked the appropriate questions in the questionnaire and get the correct self-care advice. All the information stored on the study server and the mobile phone is encrypted and securely stored, in line with data protection legislation, meaning it cannot be read by anyone else except health professionals and the researchers involved in the study. Only your name will be displayed on the device.

All non-anonymised information (i.e. personal data that can be used to identify you; e.g. hospital number, name, date of birth, and contact details including your home address and telephone numbers) will be stored securely for 5 years after the last contact between the research team and yourself according to standard Information Governance (ISO 27001) and NHS Information Governance Toolkit safeguards. All anonymised information (e.g. your responses to the study questionnaires) will be stored securely for 10 years according to University of Surrey policy. The procedures that will be

followed for the collection, storage, protection, retention and destruction of all information comply with national and EU legislation.

Should you require the details of the information held about you in electronic form during the study or this information to be removed from electronic storage during the study, please contact Docobo Ltd by phone on +44 1372 456673, or by email using the address technicalsupport@docobo.co.uk.
For all patients participating in the study (both mobile phone and normal care groups), your medical records may be inspected by the team organising the research for purposes of checking the data. In addition, your medical notes may be looked at by appropriate individuals from the hospital, the University of Surrey, from regulatory bodies or from the organisation co-ordinating the study, where it is relevant to your taking part in this research. In addition, data collected during the study may be looked at by responsible representatives from the sponsor (University of Surrey) for the purposes of monitoring and auditing to ensure that the study is being conducted properly. If you provide your consent, your General Practitioner (GP) [*please note this term will be updated to reflect appropriate personnel in each participating country*] will be sent a letter, telling him/her that you are taking part in this project.

However, if at any point during this part of the study you disclose that you are at risk of harm, with your permission, the research team would report this to your clinical team. Your clinical team will discuss with you what type of support may be appropriate for you and who else may need to have this information.

The research team would also like to use anonymised data collected from patients in this study for the purposes of secondary data analysis. You will not be able to be identified from any of the data used for this purpose. However, this data may be sent to other European countries or the United States of America, where Data Protection regulations may not be as stringent as in the UK. This data will be used primarily for the purposes of symptom management and supportive care research. It is anticipated that this data will contribute to research that has the impact to improve the patient experience of cancer, improve patient outcomes and inform cancer service delivery.

As part of the study, we have also been requested to share your anonymised responses regarding your work status and productivity with the developer of the questionnaire (i.e. Work Limitations Questionnaire). The developer (i.e. Tufts Medical Centre), who is based in the United States of America, aims to use this data to further refine the questionnaire. Your responses will be anonymised and treated with confidentiality based on an official agreement with the developer. Your anonymised responses will be linked to a random patient ID before being provided to Tufts Medical Centre. The data will be treated, processed and protected as personal data. It is up to you whether or not you agree to your questionnaire responses being sent to the developer, but your decision will have no effect on your rights or the standard of care you receive. If you do not want your questionnaire responses to be sent to the developer, then you have the option to opt out by leaving the box on your consent form relevant to this matter blank; your treatment and care will not be affected in any way.

Finally, we may contact you in the future to invite you to participate in follow-up studies to this project, or in future studies of a similar nature. In order to contact you, we will need to access your contact details, which we will store securely as part of this study. We may also use your contact details to check with your hospital and/or GP/oncology consultant/family doctor [*equivalent to be substituted*]

your health status so that we do not disturb you if you feel too unwell to take part. Your contact details will be used with strict confidentiality. It is up to you whether or not you agree to us accessing your information and contacting you in the future, but your decision will have no effect on your rights or the standard of care you receive. If you agree to us accessing your contact details and wish to be contacted in the future, you can mark the relevant box on your consent form. If you do not agree to us accessing your contact details and do not wish to be contacted in the future, then you have the option to opt out by placing a cross in the box on your consent form relevant to this matter; your treatment and care will not be affected in any way.

What will happen to the results of the study?

The overall results of the study will be used to provide information to determine whether the use of the mobile phone system is better or worse than current care in the reporting and management of chemotherapy related symptoms during and for one year following treatment.

Who is organising and funding the research?

This study is being led by a team of researchers in the University of Surrey. It is being funded by the European Commission under the Seventh Framework Programme. Hospitals involved in this study may be provided with some funding to cover the additional costs incurred in facilitating the study.

Who has reviewed this study?

The *[insert]*, which has the responsibility for scrutinising proposals for medical research on humans in *[xxxx]* area has examined the proposal and has raised no objections from the point of view of research ethics. It is a requirement that your records in the research, together with any relevant records, be made available for scrutiny by monitors from the University of Surrey and NHS *[insert Health board area]*, whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

Contact for further information?

Should you wish any further information about the project, please contact:

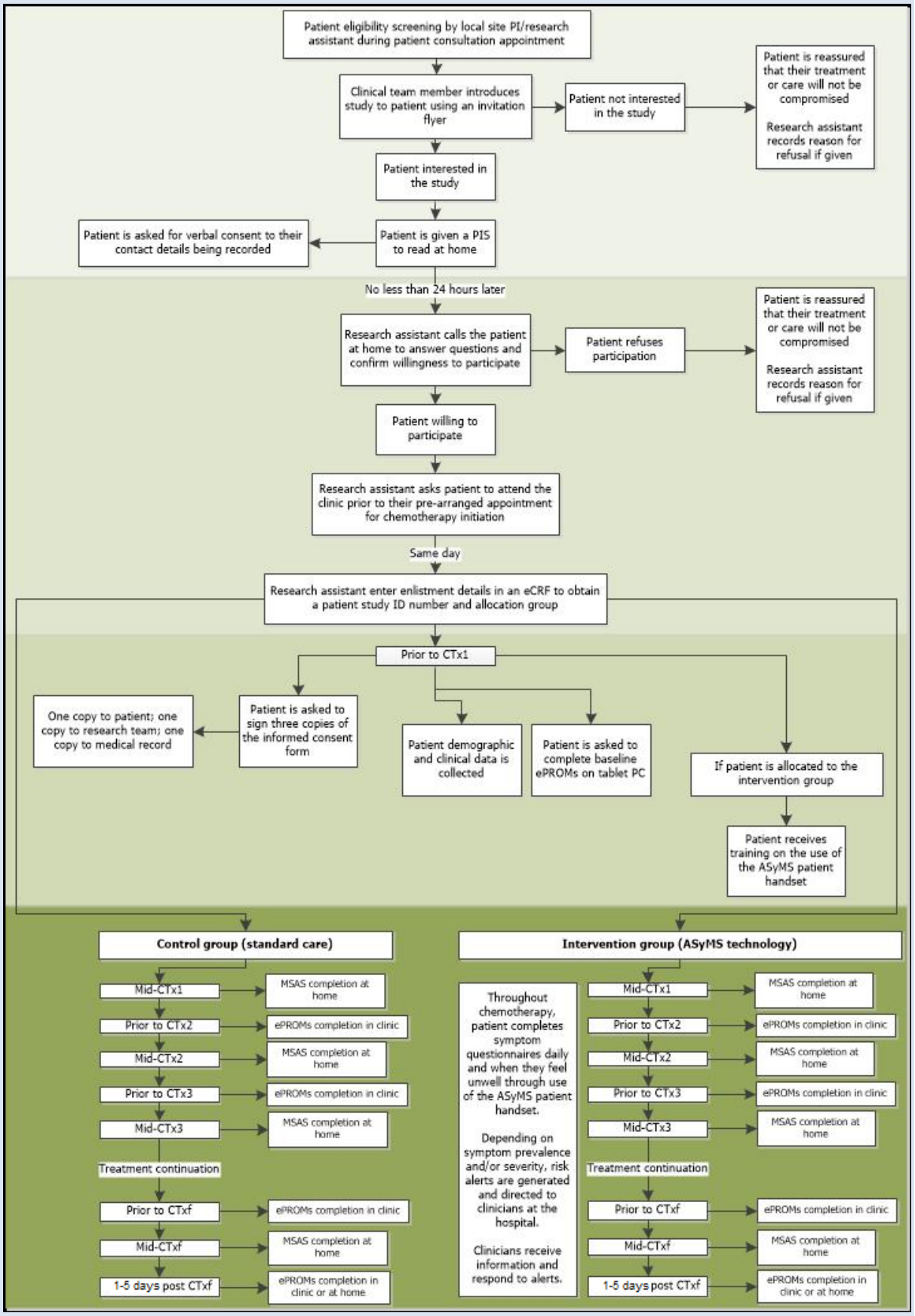
Insert name of 2 local contacts here: medical and nursing

If you would like to report a problem or a complaint about this study to someone out with the research team, please contact:

Dr Katriina Whitaker
Senior Lecturer and Lead in Cancer Care
School of Health Sciences, Faculty of Health & Medical Sciences
University of Surrey , Guildford, Surrey, United Kingdom, GU2 7XH
T:+44 (0)1483 68 4622 Email : k.whitaker@surrey.ac.uk

Thank you very much for taking time to read this information sheet.

APPENDIX 4 Schematic of data collection time-points and procedures during the intervention phase



APPENDIX 5 eSMART RCT Data Analysis Plan

RCT: The statistical analysis of the data obtained from this study will be the responsibility of the Surrey Clinical Trials Unit (CTU) in conjunction with University of Dundee.

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.

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.

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.

Active Treatment Phase

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 are missing-at-random (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).

Follow Up Phase

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-chemotherapy 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).

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.

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.

Cost-effectiveness

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.

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.