PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The eSMART Study Protocol: A Randomised Controlled Trial to Evaluate Electronic Symptom Management Using the Advanced Symptom Management System (ASyMS) Remote Technology for Patients with Cancer
AUTHORS	Maguire, Roma; Fox, Patricia; McCann, Lisa; Miaskowski, Christine; Kotronoulas, Grigorios; Miller, Morven; Furlong, Eileen; Ream, Emma; Armes, Jo; Patiraki, Elisabeth; Gaiger, Alexander; Berg, Geir V; Flowerday, Adrian; Donnan, Peter; McCrone, Paul; Apostolidis, Kathi; Harris, Jenny; Katsaragakis, Stylianos; Buick, Alison; Kearney, Nora

VERSION 1 - REVIEW

REVIEWER	Annie Lau Macquarie University, Australia
REVIEW RETURNED	24-Nov-2016

GENERAL COMMENTS	This manuscript describes a RCT protocol of an advanced symptom management system designed for patients with cancer across 5 countries. This is a very ambitious project – both in scale and in scope. The protocol is carefully-planned and the manuscript is well-written. I have a few questions to clarify aspects of the protocol and the intervention. - Was the RCT designed according to CONSORT? If so, please provide the completed CONSORT checklist - Is MSAS a validated scale? - Are the questionnaires available in different languages? What about content in the intervention for patients and clinicians? If so, what steps are in place to ensure consistency in language translation? - Is the study powered enough to detect significant changes in secondary outcomes too? (Not just the primary outcome) - What kind of clinicians will be alert handlers? Nurses only? Consultants? Residents/Registrars? How would that affect their workload? Will additional clinical staff be employed to manage the potential additional workload? - While the steps of how the intervention are outlined, please provide a diagram in the manuscript to illustrate how the intervention will facilitate interaction between patients and clinicians, as well as screenshots of what will the patients and alert handlers see on their devices.

	- Please also provide in Appendix an example of an automated self-help advice, the questions asked to elicit patient self-reported outcomes, the alert trigger message, the alert triage algorithm, and the protocol for handling the alerts. - How would clinicians receive the alerts? Will their devices beep? Are there strategies in place to manage the interruption and the increase in workload? - How would questionnaires be administered during the follow-up period? What strategies will be in place to prevent loss-to-followup or dropoff? What strategies are in place to prevent dropoff or loss-to-follow up amongst control participants? - How long would questionnaires be? What strategies are in place to prevent questionnaire fatigue? - In situations when patients use the eSMART system outside the chemotherapy session, will clinicians still respond to the trigger of alerts? Is there a protocol? - Why are only 30% randomly selected to complete the midway chemo cycle questionnaire? What is the purpose of this questionnaire? Why not all participants? Will control group participants be completing this questionnaire too? - What strategies are in place to ensure successful implementation of this patient-clinician system across different hospitals in different countries? (e.g. IT system, healthcare facility readiness, barriers and facilitators of administrators, clinicians and patients etc.)Will an implementation strategy and perhaps a process evaluation be designed to guide this?

REVIEWER	Dr Penny Wright Section of Patient Centred Outcomes Research Leeds Institute of Cancer and Pathology UNiversity of Leeds UK
REVIEW RETURNED	24-Nov-2016

GENERAL COMMENTS	This is a clearly written paper which provides a detailed picture of the study protocol including background, aims, design, analysis plan and dissemination plan. It has received ethical approval for running at the sites in the different European countries involved in the research. I have a few minor comments: 1. I think the authors should be wary of making too strong a claim about the ASyMS system. They state on page 3 line 34 that “To date, the most evolved remote monitoring system to assess and manage CTX toxicities is the Advanced System Management System (ASyMS).” Around the world there are a number of systems used for monitoring patient symptoms during and after treatment. They vary considerably with some being linked to electronic patient records (not the case with ASyMS) and some having real-time alerts as described in the protocol. There is a useful review: Review of Electronic Patient-Reported Outcomes Systems Used in

	Cancer Clinical Care, Jensen et al, Journal of Oncology Practice, JULY 2013. I recommend changing this to a more general statement. 2. I was surprised to see no reference to the Journal of Clinical Oncology publication reporting the outcomes of a very similar trial undertaken in North America: Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. Basch et al. JCO, VOLUME 34, NUMBER 6, FEBRUARY 20, 2016. 3. The primary and secondary outcomes are determined by statistically significant differences in scale scores. Is there any information about how clinical significance (and therefore meaning) relates to statistical significance in the outcome measures employed? 4. I was unsure if the patients eligible for the study were being treated with curative intent only (page 6). I realise the haematology patients may be harder to 'classify' in this way. 5. Page 8: Who are the clinicians? Are the doctors (consultants, registrars, recently qualified doctors etc.) or nurses (clinical nurse specialists, ward sisters etc.). I presume the dedicated ASyMS handset which receives the alerts will be passed on from clinician to clinician over the 24hours. Are there any issues of concern about more junior staff holding the device (particularly if on a night shift)? 6. Page 9: There is good explanation about what clinicians should do if the technology fails. I wondered if patients were not aware of a technology failure but had completed an assessment indicating severe problems how this would be managed by the clinical staff in real time (they would not know the severity rating) and the issue monitored. 7. Page 10: Will the analysis include an adjustment for the mode of data collected? Those using the telephone interview for PROMs completion may be different from others who opt for direct input themselves via the secure web link.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:
This manuscript describes a RCT protocol of an advanced symptom management system designed for patients with cancer across 5 countries. This is a very ambitious project – both in scale and in scope. The protocol is carefully-planned and the manuscript is well-written. I have a few questions to clarify aspects of the protocol and the intervention.

Specific comments:
1. Was the RCT designed according to CONSORT? If so, please provide the completed CONSORT checklist.

We followed the guidance set out by BMJ Open for protocol submissions which recommends use of the 2013 SPIRIT (Standard Protocol Items for Randomized Trials) 2013 statement recommendations. The SPIRIT checklist is included.

2. Is MSAS a validated scale?

The MSAS is a reliable and valid instrument for the assessment of symptom prevalence, characteristics and distress in oncology patients. We recognise that this was not explicitly stated in the manuscript and have now clarified this in the section 'Methods and Analysis' on page 4 of the manuscript.

3. Are the questionnaires available in different languages? What about content in the intervention for patients and clinicians? If so, what steps are in place to ensure consistency in language translation?

We agree with the reviewer that successful translation and linguistic validation of the PROMs questionnaires is necessary for consistency and confidence in study outcomes. This body of work was carried out in Part 1 of the eSMART study and we have updated the manuscript on page 4 to allude to this important step.
We have not included explicit details in this manuscript as to how the translation was done (we are constrained by word count and also by the scope of the current manuscript). However, for further clarity for the reviewer, the PROM questionnaires selected for use in the study were initially checked for availability for targeted languages (German, Greek and Norwegian). Where a translated version was available, this was obtained from the questionnaire authors. Where no translated versions existed, these were translated as part of eSMART through a rigorous translation and linguistic validation process by a company which met the following requirements: (i) compliance with International Society for Pharmacoeconomics and Outcomes Research (ISPOR) translation/validation guidelines (ii) prior experience in the translation/validation of patient-reported outcome measures as documented through previous collaborations/completed projects (iii) documented reliability/trustworthiness based on testimonials and (iv) acceptable costs and turnaround times to ensure project cost-effectiveness. When additional materials required translation locally (participant information sheets, consent forms, etc.), translations were done through dialogue with clinicians and undertaken by bilingual health professionals at the respective sites.
This work has been written up in a separate paper, detailing the methodological approach that was adopted in Part 1 of eSMART to set up this large-scale, multinational eHealth RCT.

4. Is the study powered enough to detect significant changes in secondary outcomes too? (Not just the primary outcome)

As the primary outcome is the main hypothesis, the sample size estimation was built around the primary outcome only. Tests for secondary outcomes are generally considered as 'hypothesis generating' and so we did not consider them for sample size estimation or power. Their main function is to provide backing evidence of consistency and also to point to potential mechanisms. If the primary outcome is not statistically significant but some secondary outcomes are (with a p-value < 0.05), then this provides additional evidence (the caveat being that the p-value has to be interpreted with caution given that it is secondary and there may be problems of multiple testing). See Pocock SJ & Stone GW. The primary outcome fails – What next? NEJM 2016; 375: 861-870.

5. What kind of clinicians will be alert handlers? Nurses only? Consultants? Residents/Registrars? How would that affect their workload? Will additional clinical staff be employed to manage the potential additional workload?

The protocol does not specify who is designated to handle the alerts. This decision was deliberate as although the eSMART study was designed as a nursing-led intervention and symptom management is a key aspect of the cancer nurse's role, the use of the word "clinician" means that alert handling is not restricted to nurses only, it may be an interdisciplinary role. This practical aspect of the trial was

left to each individual clinical site to determine according to their existing local policy and standard practice for symptom assessment and management. The study co-investigators in each country had regular meetings with their respective clinical site partners prior to the commencement of the study with a view to providing sufficient detail about the trial process (including the requirement for alert handlers on a 24/7 basis) in order to inform decisions around such logistical issues related to the study.
Managing the potential additional workload is key to the success of this trial and this was discussed with each clinical site at the outset. In person, presentations were made by the study co-ordinators (University of Surrey) to key stakeholders (local site PI/medical and nursing professionals) at each clinical site to provide detail on all aspects of the trial and the anticipated requirements in terms of clinical staff involvement (e.g. the role of alert handlers on a 24/7 basis and the supports in place to facilitate this). Each clinical site was given their preference of the 'pay per patient model' (x amount per patient recruited versus hiring additional research nurses/assistants for this trial).

6. While the steps of how the intervention are outlined, please provide a diagram in the manuscript to illustrate how the intervention will facilitate interaction between patients and clinicians, as well as screenshots of what will the patients and alert handlers see on their devices.

As recommended, we have now included Figure 1 as an illustration of the eSMART model of care, including screenshots of the patient and clinician devices.

7. Please also provide in Appendix an example of an automated self-help advice, the questions asked to elicit patient self-reported outcomes, the alert trigger message, the alert triage algorithm, and the protocol for handling the alerts.

Due to restrictions placed by IP and copyright, we are unable to provide the level of information requested as an appendix to this paper as this information is not currently within the public domain to protect the integrity of the study. The intellect behind the ASyMS system has been developed by certain members of the consortium over a number of years and although the information in the self-care advice, algorithms and symptom protocols are directly informed from the evidence base and clinician knowledge, these remain protected by current IP arrangements.

8. How would clinicians receive the alerts? Will their devices beep? Are there strategies in place to manage the interruption and the increase in workload?

We have clarified the alerting function of the devices on page 8 of the manuscript.
The intervention is designed to fit in with current clinical practice as much as possible, by giving clinicians the opportunity to answer alerts in a timely but manageable manner. The alerts are graded (red and amber) in terms of symptom severity: urgent red alerts have a 30 minute time window to be addressed by the clinicians, whereas amber alerts have an 8 hour period in which to be answered. Amber alerts also permit the clinician to use their own judgement to determine whether or not to call the patient following a review of the patient's symptom information on the ASyMS website. This is to allow the clinician to prioritise their workload appropriately and use their own clinical judgement when handling incoming alerts.
We have amended the manuscript on page 8 in order to reflect this.
While it is acknowledged that there may be an increase in workload through the generation of red and amber alerts, it should also be noted that the red alerts would likely have to be addressed regardless as patients' phone in as instructed if they develop serious symptoms such as fever and severe diarrhoea. In addition, in receiving evidence-based, self-care advice in real-time, it is anticipated through eSMART that lower grade symptoms may be effectively managed so that they do not advance to a higher grade which may require intervention.

9. How would questionnaires be administered during the follow-up period? What strategies will be in place to prevent loss-to-followup or dropoff? What strategies are in place to prevent dropoff or loss-to-follow up amongst control participants?

For flexibility, patients are given a choice of answering via an email link to an online version as well as telephone and returning to the clinical site. For the online questions, two reminders will be sent to non-responders (at 14 and 21 days after the due date) in order to encourage continued participation. Data collection throughout the follow-up period can be monitored via the eSMART website at a local level and also centrally to ensure participants are still inputting data. Participant retention targets will be continually reviewed and set throughout the RCT and follow-up period. We have made changes to the manuscript on page 11.

10. How long would questionnaires be? What strategies are in place to prevent questionnaire fatigue?

It should be noted that the participant information sheets explicitly state that completion of the PROMs may take 40-60 minutes so that participants are aware of the time commitment at the outset. In addition, measures have been taken to prevent questionnaire fatigue. The manuscript has been updated on page 11.

11. In situations when patients use the eSMART system outside the chemotherapy session, will clinicians still respond to the trigger of alerts? Is there a protocol?

The eSMART system is designed to facilitate communication between the participant and their clinical team 24 hours per day, 7 days a week. Each clinical site works out how to arrange a schedule of alert handlers to cover this.

12. Why are only 30% randomly selected to complete the midway chemo cycle questionnaire? What is the purpose of this questionnaire? Why not all participants? Will control group participants be completing this questionnaire too?

The mid-cycle MSAS was chosen as an additional measure to capture data during the nadir period when participants are most likely to experience chemotherapy related side effects. We believe this will provide valuable additional symptom information which may not be captured otherwise.
A sub-sample of 30% only (comprising both control and intervention participants) was chosen as while the collection of this data was considered important for the study, there was no formal sample size calculation as this is a secondary outcome yet still useful for interpretation. It was recognised that collecting this data from all participants would be significantly more time consuming and costly. It requires additional work on the part of the participant and the research team as this data is collected at a time point when the participant would not usually be in contact with the hospital/clinic.

13. What strategies are in place to ensure successful implementation of this patient-clinician system across different hospitals in different countries? (e.g. IT system, healthcare facility readiness, barriers and facilitators of administrators, clinicians and patients etc.)Will an implementation strategy and perhaps a process evaluation be designed to guide this?

This is a relevant point and highlights the challenges which we faced in the development and integration of an eHealth system for use within a wider European context. We acknowledge the need for adequate preparation prior to the RCT concerning the technology and readiness for the trial. As mentioned briefly in the manuscript (page 4), Part 1 of the trial included the necessary preparatory work required for the RCT (including feasibility testing and assessment of technological readiness to incorporate the ASyMS system at the participating sites). A crucial part of this was feasibility testing and assessment of the technological readiness of the ASyMS system at the participating sites. This

assisted the establishment of communication and consolidated relationships between the eSMART research teams and the clinical sites, effectively laying the groundwork for Part 2 (RCT). As noted above (point 5), there are regular meetings with the clinical sites to discuss additional issues and challenges relevant to the conduct of the trial as they arise.
In addition, one of the work packages (WP4) of the trial is focussed on Assessing Changes in Clinical Practice. There are two components to this: i) a full cost-effectiveness evaluation, outcomes for which are in part being assessed by the CSRI and EQ-5D PROMS that patients complete, ii) assessment of changes in clinical practice from the perspective of the clinicians directly involved in the trial by means of assessing their perceptions and use of technology at baseline (captured during Part 1 of the trial) and again at follow-up upon completion of the RCT component (in Part 2) via study-specific surveys. Survey data will be complemented by focus groups held with clinicians at each clinical site in each country too, to further explore and understand the impact of the intervention on clinical practice.
Despite the importance of the reviewer's comment, we have not addressed this specifically within the current manuscript as it forms part of a standalone, methodological paper concerning the approach taken to setting up a multinational eHealth trial.

Reviewer #2:
This is a clearly written paper which provides a detailed picture of the study protocol including background, aims, design, analysis plan and dissemination plan. It has received ethical approval for running at the sites in the different European countries involved in the research.

Specific comments:
1. I think the authors should be wary of making too strong a claim about the ASyMS system. They state on page 3 line 34 that "To date, the most evolved remote monitoring system to assess and manage CTX toxicities is the Advanced System Management System (ASyMS)." Around the world there are a number of systems used for monitoring patient symptoms during and after treatment. They vary considerably with some being linked to electronic patient records (not the case with ASyMS) and some having real-time alerts as described in the protocol. There is a useful review: Review of Electronic Patient-Reported Outcomes Systems Used in Cancer Clinical Care, Jensen et al, Journal of Oncology Practice, JULY 2013.
I recommend changing this to a more general statement.

We thank the reviewer for her comment and for bringing this review paper to our attention.
This review strengthens our viewpoint that ASyMS is among the most developed and clinically tested systems that deals with CTX toxicities. As suggested by Jensen et al. (2013) "ideally, it would be useful for e-PRO systems to monitor patients throughout the course of care while capturing detailed information about patients' responses to specific treatments in order to balance these important objectives" and also "future e-PRO systems will provide opportunities for automatic integration of PRO content tailored to individual patient needs". The ASyMS intervention incorporates many of the features identified by Jensen and colleagues as important.
We agree with the reviewer's more general comment and have modified the manuscript on page 3.

2. I was surprised to see no reference to the Journal of Clinical Oncology publication reporting the outcomes of a very similar trial undertaken in North America:
Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. Basch et al. JCO, VOLUME 34, NUMBER 6,FEBRUARY20,2016.

We agree that this recent paper reports findings which are interesting and complementary to our study and we have included reference to it in the introduction on page 3 and 4 of the manuscript. However, as pointed out by Basch and colleagues themselves, it is worth noting that there are some limitations to the STAR intervention: it was carried out in a single centre, symptom reporting was not done on a daily real-time basis, clinical actions carried out in response to patient-report were not

recorded, cost analysis was not conducted and the software did not provide recommendations to patients or clinicians on the management of reported symptoms. The eSMART intervention addresses all of the above limitations. Given the very promising results reported using earlier, more basic systems such as the STAR, we expect that eSMART will add significantly to the existing body of knowledge in this field.

3. The primary and secondary outcomes are determined by statistically significant differences in scale scores. Is there any information about how clinical significance (and therefore meaning) relates to statistical significance in the outcome measures employed?

We would like to clarify that the secondary outcomes were chosen because of their clinical and overall relevance to the study population rather than for the differences we expect. We agree with the reviewer that an arbitrary number reflecting statistical significance does not necessarily translate into something that is clinically meaningful, particularly when using an outcome measure such as the MSAS as it is less objective than a blood pressure measurement, for example. We determined our minimum clinically important difference to be 0.15 (SD 0.6) based on a previous study (Ruland et al., 2013), which translates to an effect size of 0.25 (low-moderate according to the Cohen classification).

4. I was unsure if the patients eligible for the study were being treated with curative intent only (page 6). I realise the haematology patients may be harder to ‘classify’ in this way.

Our inclusion and exclusion criteria were not chosen with the intent of recruiting patients undergoing ‘curative’ treatment only. As the reviewer rightly points out, this description is somewhat of a grey area, particularly in haematological cancers. Rather, we limited our patient group to those with non-metastatic disease because, although including distant metastases would broaden the recruitment pool, it was decided that using such a heterogenous group would result in potential problems during statistical analysis when dealing with large standard deviations (due to large variations among patient symptom profiles, i.e. treatment related versus disease related).

5. Page 8: Who are the clinicians? Are the doctors (consultants, registrars, recently qualified doctors etc.) or nurses (clinical nurse specialists, ward sisters etc.). I presume the dedicated ASyMS handset which receives the alerts will be passed on from clinician to clinician over the 24hours. Are there any issues of concern about more junior staff holding the device (particularly if on a night shift)?

Please see response to comment #5 by Reviewer 1.

6. Page 9: There is good explanation about what clinicians should do if the technology fails. I wondered if patients were not aware of a technology failure but had completed an assessment indicating severe problems how this would be managed by the clinical staff in real time (they would not know the severity rating) and the issue monitored.

We agree that this is a very important safety issue and it is addressed during patient training. Therefore we have added to the manuscript (page 9) in order to make this point clearer.
The success of the implementation of the technology is heavily reliant on good communication pathways and continuous monitoring of the data. Syncing of all devices will be monitored on a daily basis and any problems will be followed up by research staff at the clinical sites. All clinicians involved in the study have 24 hour access to a technical support site manned by the technology partner (Docobo) in this trial. Also, all academic partners can monitor the data and are available in the case of a technology failure.

7. Page 10: Will the analysis include an adjustment for the mode of data collected? Those using the telephone interview for PROMs completion may be different from others who opt for direct input

themselves via the secure web link.

This issue was taken account of in developing the data analysis plan. 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).

VERSION 2 – REVIEW

REVIEWER	Penny Wright University of Leeds UK
REVIEW RETURNED	17-Feb-2017

GENERAL COMMENTS	The authors have responded fully to my comments.