Key to Review's: ES = Editor's summary SE = Statistical editor OE = Other editors
R1 = Reviewer 1 (Katherine Ruane) R2 = Reviewer 2 (Galina Velikova) R3 = Reviewer 3 (Ethan Basch)

Rev	Point	Comment	Amendment to Paper	Page / Table / Supp File Number
ES	1a	The study was powered to detect a difference in the total MSAS score of 0.15, although there is very little discussion of the clinical significance of this difference.	Thank you for this comment. We have added further detail to the manuscript discussing the lack of known cut-off scores for MSAS to indicate clinically important change and added references to studies, in particular the one in 1b below though this study is small, and enrolled advanced cancer patients with worst pain so may be an overestimate for our population. We have also added further detail on our rationale for sample size and power calculation. The value of 0.15 was one of the few differences found in an RCT setting (Ruland et al) and hence this was the basis for the sample size calculation. The Cohen's effects size was 0.25 which would be considered low to medium. This comment is addressed with changes made within the Abstract, Methods and Discussion sections of the paper.	Pages 2;6;7;10
ES	1b	My quick read of the literature suggests that subscale differences are expected to be 0.20-0.66 to be considered clinically significant (https://ascopubs.org/doi/abs/10.1200/jco.2004.22.90140.8269), which presumably would be greater for a total score.	As above we have added this reference to the text. We have added further detail to the manuscript in relation to clinical significance within the Abstract, Methods and Discussion sections of the paper.	Pages 2;6;7;10

Rev	Point	Comment	Amendment to Paper	Page / Table / Supp File Number
ES	2a	Reviewers were cautiously enthusiastic given the challenge of symptom management during chemotherapy, but they had a number of suggestions and there are questions about the intervention, adherence to it, and whether these differences are clinically meaningful. For instance, there is no reporting on adherence to the intervention: how often did patients record symptoms (was it daily?)	Patients reported their symptoms daily via the ASyMS intervention. This information is reported inthe description of The Intervention in the Methods section as well as generally throughout the paper. A new section, Patient and Clinician Adherence to the Intervention, has been included within the Methods and Results section and details patients' compliance with the intervention. As above we have added text discussing clinical significance in the paper.	Pages 4; 6; 11
ES	2b	How often did it trigger alerts to their clinicians?	Alerts were generated to clinicians via the evidence-based clinical algorithms (example in Figure 2). The frequency of alerts was dependent upon this algorithm. Further detail explaining this component of the intervention has been added to the Methods section under The Intervention sub-heading. Also, to further address this comment, we have added some additional information in the Results section under Adherence to the Intervention and Alert Outcomes on the number of daily symptom questionnaires completed over the trial and the number of red and amber alerts generated for the intervention groups as a whole.	Pages 4;9
ES	2c	What changes were made in response - I think it's critical that this information get reported.	Detail within 'The Intervention' sub-section of the Methods section provides additional information on the intervention and communication pathways between patients and clinicians. See also Figure 1. For further context, an example of the symptom management protocol for symptoms of nausea and vomiting is now included as Figure 2.	Page 4; Figures 1 and 2

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ES	2d	We do not know if patients report feeling better because they are assessing their symptoms more frequently or because clinicians are intervening on their behalf. To this point, what was the symptom burden over time in the intervention group? I was really surprised that they did not report this.	Thank you for this comment. Symptom burden over time is reported in Table 2. Forthcoming publications reporting on qualitative data from the eSMART trial will provide insight into mechanisms of the intervention from both patient and clinician perspectives. We have included top level information from this qualitative component of the study of what elements of the intervention patients and clinicians found most impactful.	Table 2 Pages 9-10
ES	3a	The tables need work (for instance, it is unclear why tables 1 + 2 and 4+5 were separated out when they should be combined).	Thank you for this comment. We have revised our Tables and these are now as follows: Table 1: Participant characteristics at enrolment Table 2: Descriptive Summary of Primary Outcome – Total MSAS and sub-domains Table 3: Mixed-model, repeated-measures analysis of change from baseline using Gamma model Table 4: Clinician adherence to time when handling alerts Table 5: Clinical responses following ASyMS alerts Table 6: Adverse events	Tables 1 - 6
ES	3b	..and nowhere do they comment on missing data or the number of individuals completing the PROMs.	The CONSORT diagram (Figure 3) has been updated and contains details of MSAS data not collected and not analysable. This is also detailed in page 7 under the Recruitment section.	Figure 3 Page 7

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ES	3c	..This is critical since there were a lot of PROMs with a pretty massive survey burden for patients undergoing chemotherapy and we would expect a fair amount of attrition	We did have a level of attrition as detailed in the CONSORT diagram (Figure 3); however, this was lower than anticipated. Qualitative evidence (that will be fully reported elsewhere) would suggest that positive attitudes from clinical teams, seeing the impact of the intervention in practice and commitment to research likely contributed to continued reporting by participants. We have now discussed these issues in greater depth in the Discussion section.	Figure 3 Pages 9 & 10
SE	1	Conduct of the trial seems well done, but there are issues with the reporting, including that reporting of the statistical analyses are incomplete. Quite likely it'd be better if they followed the appropriate CONSORT research reporting checklist.	Thank you for mentioning this. The CONSORT diagram has been extended and the CONSORT-PRO checklist has been completed and uploaded.	Figure 3
SE	2	Trial registry did not include secondary endpoints, but the protocol described them. However, the registry has different timeframes in primary outcomes from the ones in protocol and paper. And the secondary outcomes in the protocol and paper differ too. All needs to be clarified.	Thank you for highlighting this. The appropriate update information has been provided to the Clinical Trials Registry and is awaiting their update onto their public facing platform.	N/A
SE	3	Absolute differences should be reported for all primary and secondary endpoints, not just p values.	Thank you – we have revised our abstract for primary and secondary and results sections accordingly to report these differences as required. All differences and 95% CI are in Table 3.	Pages 2; 8-9 Table 3

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SE	4	More explanation of the repeated measures analysis approach would be valuable, including why actual SDs were smaller than anticipated.	Thank you for this comment. We have discussed this and unfortunately we are unable to answer this specific question - we do not know why the SDs were smaller than expected, but a possible explanation is because we recruited a different population of patients with cancer than the original source publication. No changes have been made within the manuscript to reflect this comment.	N/A
SE	5	The hardest thing to grasp is what the primary outcome means. Looking at the MSAS it allows people to score each symptom between 0 and 4. As the total score is the simple average of all the symptom scores it too should have a maximum value of 4. The numbers reflect ordered categories typically slight, moderate, severe, very severe for magnitude and rarely, occasionally, frequently, almost constantly for frequency. The difference detected was 0.15 which would be a fraction of the step between slight and moderate, say, or between occasionally and frequently. That doesn't sound much. Another way of assessing this 0.15 is to compare it with the spread of scores at baseline. The SD was 0.3 so this difference represents about half a SD, which is traditionally regarded as a "medium" effect size. But I'm not sure how valid this rule of thumb is when the data are quite skewed, as here (the SD is almost as big as the mean).	Thank you for this comment – it relates to the previous comments from ES1a and ES1b. We have added further detail to the manuscript discussing the lack of known cut-off scores for MSAS to indicate clinically important change. We have also added further detail on our rationale for sample size and power calculation. This comment is addressed with changes made within the Abstract, Methods and Discussion sections of the paper.	Pages 2;6;7;10
SE	6	There is also a statement that states 'No statistically significant differences were found in health systems and information needs.' This needs quantifying.	The health systems and information needs is one of the domains in the SCNS-34 – we have now clarified that is one of the domains of this tool.	Page 9

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SE	7	AEs could also be better reported - in a table perhaps.	Thank you for this suggestion. We have now added Table 6 Summary of adverse events: total sample and by trial arm into the manuscript.	Table 6
SE	8	Abstract also needs work - unclear what outcome the first result relates to.	Thank you for this comment and suggestion for revision of the abstract. We have now revised the abstract accordingly.	Page 2
OE	1	Very concerned about whether these differences are clinically-meaningful.	Thank you for this comment – this comment is similar to comments received by ES1a, ES1b and SE5. As noted previously to those reviewers, further detail has been added to the Abstract, Methods and Discussion sections of the paper.	Pages 2;6;7;10
OE	2	Registry is not up to date, still listed as recruiting.	Thank you for highlighting this. The appropriate update information has been provided to the Clinical Trials Registry and is awaiting their update onto their public facing platform.	N/A
OE	3	Anticipated enrolment is 1100, not the 830 that were enrolled.	Thank you for highlighting this – we had an original and a revised Sample Size and we have now more thoroughly explained this within the 'Sample Size' sub-section within the 'Methods' section in relation to our lower than expected attrition rate.	Pages 6-7
OE	4	Registry lists 8 primary endpoints, all at different times of ascertainment. Very difficult to map these 8 primary endpoints on to what is being reported in the paper. Is a bonferonni correction needed?	There was one primary endpoint in the study and the Clinical Trials Registry has now been updated for clarity. We don't need to conduct a Bonferonni Correction as we had only one primary outcome – i.e. total MSAS.	Page 3 (reference to ClinicalTrials.gov)

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OE	5	Why were 70% of patients being treated for breast cancer? What does that mean for generalizability?	We acknowledge that more of our patient sample were diagnosed with breast cancer and were female because our clinical sites recruited more people with breast cancer. We have added further explanation of why this occurred in our Strengths and Limitations section of the Discussion and also discussed implications in terms of generalisability.	Page 12
OE	6	What does it mean that so many patients refused participation – are they not interested in remote symptom management, which has implications for the uptake of the intervention. Are these folks interested in remote monitoring, suggesting these results are a best-case scenario?	Second to last paragraph on page 11 of the Discussion section addresses the numbers of potential participants who declined to participate and the reasons for this. Our study's refusal rate is not unlike that of other similar studies (e.g. Absolom 2021 – 28%, our study 30%). While another study reported fewer people choosing to decline (e.g. Basch; 8.6%), that study involved much less onerous data collection for patients.	Page 11
OE	7	Could the authors provide more information regarding the "actual" intervention that occurred, like how many and what reports triggered self or medical interventions, what were the interventions, what were the results,etc. currently it's like a black box with only a general theoretical description in methodology section.	This comment is of a similar theme to comments from reviewer ES2a, ES2b, ES2c. Changes have been made in various sections within the manuscript including The Intervention and throughout the Results sections to provide more detail about the intervention to address those previous points and this comment too.	Pages 4; 9; Figures 1 and 2
OE	8	The inclusion criteria are quite narrow (4 cancers with 71% breast cancer, non-recurrent, non-metastatic, chemo solely for first-line use or firstly used in 5 years...), which limits the generalizability of the conclusion. Could the authors clarify the rationale for these criteria?	The 'Settings and Patients' outlines the inclusion and exclusion criteria and explains the rationale for these choices. The generalisability of the study population is also addressed in the 'Strengths and Limitations' section within the Discussion.	Pages 3-4; 12

Rev	Point	Comment	Amendment to Paper	Page / Table / Supp File Number
R1	1a	As mentioned, it was for a small subset of cancers and the majority of participants were female, so it would be good to see the results in a wider group.	Thank you for this comment, this relates also to comment OE8 and so please see the detail added within the Settings and Patient section in the Methods section to explain our choice of inclusion / exclusion criteria. In relation to seeing the results in a wider group, please also see the recommendations made in Strengths and Limitations that future research may also expand to focus on other diagnostic groups.	Pages 3-4; 12
R1	1b	I also wonder what would happen if there were people who weren't comfortable with using an app/website/English isn't their first language and how this could benefit them.	We worked with native languages in our partner countries as much as possible. Additional detail has been added to The Intervention sub-section within the Methods section explaining what aspects of the intervention were translated into native languages of our partner countries to support participation of patients and clinicians.	Page 4
R1	2	*Do you have any suggestions that might help the author(s) strengthen their paper and make it more useful for doctors to share and discuss with patients/ carers?* No I don't think so. The only thing that comes to mind is patients being reassured that their data is being held securely and no one can access it other than their clinical team.	Thank you for this comment. The patient information sheet did provide information to patients about where their data was stored and accessed. No change made to the manuscript.	N/A

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R2	1a	The intervention is described in general terms. There is no information provided on the fidelity (or adherence) of the intervention by patients or clinicians. It would be very helpful for the reader to have a better description of the intervention in a supplement online file. This could be an example of one chemotherapy-related symptom that was included for daily monitoring with its range of responses as well as an example of which symptoms or combination of symptoms would generate a red alert.	Thank you for this comment – it is of a similar theme to comments from reviewer ES2a, ES2b, ES2c and OE7. Changes have been made in various sections within the manuscript to provide more detail about the intervention to address those previous points and this comment too We have also added information on patient and clinician adherence to the intervention in The Methods and Results Sections.	Pages 4;6; 9 Figures 1 and 2
R2	1b	In terms of adherence to the intervention, it is essential to have some high-level information on how many reports were completed. Reporting daily is quite a bit ask for patients. How many patients did adhere to the daily reporting, how many reports per patient were generated and over what time period? Similarly, how many red and amber alerts were generated and, if possible, some indication as to whether clinicians responded to these or not? In most of these complex interventions, the authors would like to publish separately more detailed information on the intervention adherence but, for this main manuscript, it is essential to have some key data on its use by patients and clinicians. This information will help to understand the results of the study and also is essential when considering future implementation.	Thank you for your comment. We agree that providing information about intervention adherence is important for future implementation of such interventions. Additional information has been provided on Adherence to the Intervention on Page 9 – this provides information on patient and clinician adherence to the intervention.	Page 9

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R2	2	Information on missing outcome questionnaires is not provided at all. The authors have reduced the sample sizes as the attrition rate was lower than predicted. However, I believe the CONSORT diagram should include the number of completed outcome questionnaires at each time point and how many were analysed. The authors mention that they treated the data as missing at random (MAR) but there is no justification why this conclusion was made. My strong recommendation is to include the number of outcome questionnaires completed by patients at each time point in the CONSORT diagram and also provide some justification for treating the data as missing at random. Judging from Table 3, about 60% of baseline measures were returned in the intervention by cycle 5 and <50% by cycle 6. This could be because the patients stopped their chemotherapy and came off the study or it could be that they didn't attend the clinics to complete the online forms. This information should be included in a separate section looking at the missing data as a proportion of that expected (you may refer to Coens C et al. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. Lancet Oncol. 2020 Feb;21(2):e83-e96. doi: 10.1016/S1470-2045(19)30790-9).	We have included this information for the MSAS but not for all secondary outcome measures given this would expand the CONSORT diagram considerably.	Figure 3

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R2	3	From the description of study design, it is not clear what was the duration of the study. Was it a fixed time in months or more variable length as the duration of six cycles of chemotherapy? I note that some patients received 12 cycles or more. What was the formal end of the study? If this was left flexible for pragmatic reasons then information should be provided on how long each patient was on the trial.	Thank you for this comment and requesting clarity on this important issue. We have now added some further clarification and detail on the length of time patients participated in the trial in relation to receiving chemotherapy treatment. This clarification has been added to the start of the Methods section and the 'Settings and Patients' sub-section within the 'Methods' section. Further information is provided in the Results section.	Pages 3; 5; 7
R2	4	Title: is too long and could be reduced with the extended definition of eSMART and/or ASyMS provided in the abstract of the manuscript.	Thank you for this suggestion – we have now revised the title of the paper slightly to shorten it. The new title of the paper is: 'Real Time Remote Symptom Monitoring During Chemotherapy for Cancer: Results from eSMART, A European Multicentre Randomised Controlled Trial'	Page 1
R2	5	Abstract: The abstract doesn't specify for how long the daily reporting was required to be continued by patients and what is the trial duration. The abstract describes the results from the primary endpoint but does not mention the secondary outcomes. The abstract should cover all results including primary and secondary secondary patient reported outcome measures, as well as the clinical outcomes (neutropenic sepsis rate and hospital admissions).	Thank you for this comment and suggestion for revision of the abstract. We have now revised the abstract accordingly to report this additional information.	Page 2

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R2	6	Introduction, page 3: Please replace references to the eRAPID RCT (Velikova, 2020) to the now fully published manuscript (Absolom K…Velikova G, J Clin Oncol. 2021 Mar 1;39(7):734-747. doi: 10.1200/JCO.20.02015. Epub 2021 Jan 8.). Furthermore, in the discussion some of the published data will be worth comparing with the present study.	This is now on page 3 and the change has been made. The suggested Absolom et al 2021 reference for the eRAPID RCT has been incorporated where relevant throughout the paper.	Page 3
R2	7a	Methods Section: page 4: Exact dates of study start and end usually are required to be provided rather than years.	Thank you for this comment. Specific recruitment start/end dates for the trial have now been included in Page 3 (Methods).	Page 3
R2	7b	Methods Section: Page 5: Why did the authors exclude patients who received weekly chemotherapy?	A statement of rationale for the exclusion of participants receiving weekly chemotherapy regimes has now been added to page 4: i.e. '*or weekly chemotherapy 'as timeframes covered by the outcome measures were incompatible with weekly administration.'*	Page 4

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R2	7c	Outcomes (CONSORT item 6a): The authors have completed and defined a pre-specified primary outcome measure (MSAS). There's less detail on how long the outcome measure was actually assessed for. Primary time point is not defined at all. The analysis is based on all longitudinal data. The metric which was applied is both the total score of 7 MSAS and change from baseline. Several MSAS scales were analysed, it may be stated more clearly that the primary outcome was MSAS GDI. Please provide the range of scores for MSAS GDI and the sub-domains. A good detailed description is provided on the primary and the secondary patient reported outcome measures, however, there are no details on how the clinical measures were collected such as adverse events, neutropenic sepsis and hospital admissions. This information should be provided in the methods.	Thank you for this comment. There is more detail of length of follow-up added to the text which was up to 6 cycles and most 4-6 depending on treatment and cancer. There is no primary time as an endpoint as this would be arbitrary and we need a global test of efficacy. The question is why should one arbitrary timepoint be important? I agree this is often used in studies and is agreed by statisticians as a poor way of analysing the effect of a trial intervention for data over time when no particular timepoint is 'primary'. Individual t-tests at each time point can be biased and assume data is MCAR which is unlikely. Using mixed models assumes data is MAR and uses all available data. For these reasons we used a single global test of difference between the two treatments over all time points. (Repeated Measures in Clinical Trials: Analysis using mean summary statistics and its implications for design. Frison and Pocock Statist Med 1992; 11: 1685-1704. The primary outcome was stated as the Total MSAS. The GDI was a sub-domain and is a secondary outcome and stated in the text. The range of scores for all domains have been added to the tables. We have now included a section on Adverse Events which details this requested information.	Pages 6-7; Table 6

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R2	7d	Sample size (CONSORT item 7a): There is a clear description of how sample size was determined but subsequently the original sample size was modified because the observed drop-out rate was only 10% when the sample size allowed for 30% drop-out rate. This is referring to the formal withdrawal from the trial but there is no data on what was the completion rate of the outcome questionnaires. From one of the tables, it is obvious that the non-completion rate at six cycles appeared to be <50% of the baseline. See further comments under major comments missing data above	Thank you for this comment. We have added detail on the MSAS and completion rate of questionnaires. We did this did this only for MSAS as the primary outcome, and not the secondary outcome measures as this would require separate CONSORT diagrams for each PROM and each associated sub-domain. Within the MSAS CONSORT diagram, we report on data relating to people who had died, withdrew (planned or unplanned) and MSAS unanalysable. Because patients participated for up to a maximum of 6 cycles, 50% of data is not missing at cycle 6 – but most people did up to cycle 4 – this reflects what happened in practice.	Figure 3
R2	7e	Sequence generation (CONSORT item 8a): Randomisation is described reasonably well. It's not clear what is meant by "standard GCP compliant methods were used to generate random allocations". This needs to be clarified.	This statement has been taken out. Randomisation was completed by the Surrey Clinical Trials Unit, please see the text on Page 6: '*Randomisation was performed remotely and independently by Surrey Clinical Trials Unit (a UK CRC registered CTU).'*	Page 6
R2	7f	Blinding (CONSORT item 11a): The study is not blinded as the intervention could not be blinded to the patients or the healthcare providers. It's not clear what is meant by "blinding of evaluators was achieved". In the discussion, the authors mention that statisticians were blinded to the study arm but this should be described more clearly in the methods section.	This has been addressed with this added clarity in the Randomisation and Blinding section.	Page 6
R2	7g	Outcomes and estimation (CONSORT item 17a): The authors have provided sufficient detail on the primary outcome results for each of the groups and the estimated effects with 95% confidence intervals.	Thank you for this comment – we have taken no further action on this point.	N/A

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R2	7h	Harms (CONSORT item 19): The authors report the number of deaths in each arm. The protocol specifies that the independent data monitoring committee was monitoring safety but no information is provided on how frequently this was done.	Thank you for this comment – we have now added details of the frequency of the DMC meetings (i.e. on average 6-monthly) under the Methods section.	Page 3
R2	8a	Results section: Table 1: Please clarify in the table what is meant by mid-cycle PROMS as a footnote. This becomes clear from the text but the table should stand on its own. Why did some patients have up to 12 cycles of chemotherapy: again, please explain either as a footnote or in the text.	This reference was an error – this refers to data not specifically related to the primary or secondary outcome measures and so we have removed reference to it here.	N/A
R2	8b	Results section: Table 2: Perhaps it's worth noting in the text that the intervention arm happened to have a higher education level with more university degrees.	Education level has been included within the text within 'enrolment characteristics' in the 'Results' section.	Page 8
R2	8c	Results section: Table 3, Total MSAS GDI: could you please provide information on the range of score. This is not provided in the text or in the protocol and it's important to know the range in order to understand the differences.	Table 2 contains information on the range of scores for the GDI and other sub-domains.	Table 2

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R2	8d	Results section: Table 4: The title should specify this is referring to the primary outcome measures. Similarly, table 5 should specify that it refers to secondary outcome measures.	Table titles have been revised and clarified and the primary outcome measure identified in Table 2. The revised list of tables are: Table 1: Participant characteristics at enrolment Table 2: Descriptive Summary of Primary Outcome – Total MSAS and sub-domains Table 3: Mixed-model, repeated-measures analysis of change from baseline using Gamma model Table 4: Clinician adherence to time when handling alerts Table 5: Clinical responses following ASyMS alerts Table 6: Adverse events	Tables 1 - 6
R2	8e	Results section: Figure 2 should specify the range of scores on MSAS as above	Thank you for this comment. We have considered this request but respectfully disagree as normally the range of scores would not be included in a graph. We do, however, report the range of scores in Table 2.	Table 2
R2	8f	Results section: Figure 1, CONSORT diagram – please add the number of returned outcome questionnaires at baseline either at each cycle or at least at cycle 6 which seems to be the main time point for the primary outcome. This will then generate the numbers actually analysed.	The CONSORT diagram has been updated to include this information.	Figure 3
R2	8g	Results, page 9, line 54, WLQ questionnaire results: The way this paragraph is structured leads to overinterpretation. The message is that there were no between-group differences and trends perhaps should not be discussed in detail. Suggest to re-phrase.	Thank you for this comment – we have revised this statement slightly and do include a cautionary statement for interpretation of this result in the Discussion section.	Page 11

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R2	8h	Page 10, line 1-10: The authors need to add details to methods as to how data on adverse events, planned and unplanned hospital admissions was collected. It is interesting also to note that, despite the higher neutropenic events in the intervention group, the hospitalisation number was not higher. Overall it looks like the total number of hospital admissions is rather low for this large patient population. Definition of neutropenic event should be provided as well.	Detail on the collection of Adverse events and definition of neutropenia have been incorporated within 'outcome measures' within 'methods'.	Page 5
R2	9a	Discussion section: The discussion is detailed and the authors have made extensive comparisons with available literature, outlining what is innovative in their study and its main contributions. I would encourage them also to discuss that this is perhaps the largest up-to-date study of remote monitoring of symptoms during chemotherapy for cancers being treated with curative intent. It is worth mentioning that, even though they had Hodgkin's and non-Hodgkin's lymphomas with metastatic disease, in the majority of those cases, the purpose of the chemotherapy is still to achieve a cure. This is a further strength in addition to those outlined by the authors.	Thank you for this feedback. We have emphasised this as a strength of the study in the start of the Discussion and 1st paragraph of 'strengths and limitations'.	Page 12
R2	9b	Discussion section: I recommend to include as a reference the recently published eRAPID trial by Velikova, et al and replace the current reference which is based on a presentation at ASCO.	This reference has been updated throughout the manuscript.	Throughout manuscript as appropriate.
R2	9c	Discussion section: Page 10, line 30: The statement that this is the first study to assess changes in symptom burden over time is perhaps not entirely correct (). Studies by Basch, Denis and Velikova have also looked at changes in symptom burden over time. Please rephrase.	Thank you for this suggestion. This phrase has now been re-phrased in the Discussion.	Page 9

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R2	9d	Discussion section: Page 10, line 38: Please rephrase the first sentence which currently states that reduced symptom burden was associated with significant improvements in anxiety etc. This form of words suggest causation which the authors correctly say they can't claim on the basis of this study design. Perhaps it's better to say "remote symptom monitoring was associated with improvements in anxiety etc".	Thank you for this suggestion. This paragraph has now been re-phrased to remove the suggestion of causation as noted by the reviewer.	Page 10
R2	9e	Discussion section: Page 11, paragraph 8-12: The eRAPID trial is now published in full and the results are not preliminary, so please remove "preliminary" and replace with the new reference.	This reference has been updated throughout the Discussion.	Page 9
R2	9f	Discussion section: Page 11, line 49: Please state clearly that work limitations were not different between the two groups. Trends should not be reported.	The text has been rephrased as follows and we have not reported trends - "*Work limitation scores were not statistically significantly different between the two groups ".*	Page 11
R2	9g	Discussion section: Page 11, line 58: There's a statement here "no device-related incidences reported" which contradicts one of the limitations mentioned when the system was offline. Perhaps remove this sentence. In the same paragraph, the statement that trials have not measured neutropenic events in the intervention control group is not entirely correct as the eRAPID trial looked at chemotherapy delivery and hospital triage including for neutropenic evens (Absolom et al 2021). Just rephrase, please, and remove the sentence that "recent comparisons cannot be made with existing literature".	Thank you for this comment. This has been rephrased and the reference to Absolom et al has been removed. This has been clarified in the text. The fault was related to the SIMs and communication network and through extensive testing we confirmed that this was not device related.	Pages 5;9;12
R2	9h	Discussion section: Page 13, line 17, Implications for clinicians in policies: I would recommend that authors state clearly in the first sentence that the recommendations should be made for patients with cancer treated with curative intent. This is a real strength of the study and it should be emphasised.	Thank you for this comment. We have emphasised this as a strength of the study in the 1st paragraph of 'strengths and limitations'.	Page 12

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R2	9i	What is already known about this topic: I would recommend to rephrase the third point to state that remote monitoring interventions are available and have been studied in advanced/metastatic cancer but very few were evaluated in cancers treated with curative intent.	Thank you for this suggestion. This has now been rephrased to: *'Digital remote monitoring interventions to support patients with chemotherapy are available but very few were evaluation in cancers being treated with curative intent'*	Page 14
R3	1a	The clinically meaningful score change for the primary outcome would ideally be described in this paper in the Methods section, and if available for subscales or secondary measures.	We have added further detail to the manuscript in relation to clinical significance within the Abstract, Methods and Discussion sections of the paper.	Pages 2;6;7;10
R3	1b	A responder analysis could be added, to supplement the comparison of means. This would be an analysis that reports the proportion of patients at each cycle in each arm who experienced a clinically meaningful benefit in the outcome compared to baseline.	Following consideration, the Study Team feel that responder analysis would not necessarily be balanced in terms of randomisation and so is not a good way of determining efficacy. It also has issues with defining 'response' and there is no agreed method to decide this, especially a 'meaningful response'. We agree this could be analysed as a post hoc question but would take considerable time and add to an already lengthy analysis. No changes have been made to the manuscript.	N/A
R3	2	Related to the above, perhaps you could provide some description in Results (page 10, line 3) how to conclude if a difference of -.015 is meaningful?	Clinical significance/meaning is addressed in the 'discussion' and explanations around the conclusions have been provided.	Page 10

Rev	Point	Comment	Amendment to Paper	Page / Table / Supp File Number
R3	3	P-values ideally would be added for each cycle for the comparison of intervention and control mean scores for that cycle in Table 3.	Following consideration, the Study Team respectfully disagree with this request as this would give a substantial number of secondary tests. Multiple testing is not a good way of analysing repeated measures or reporting. The main analysis used a global test over all time periods and hence gives a better and simpler single hypothesis for the primary analysis. No changes have been made to the manuscript.	N/A
R3	4	There is a new paper by Velikova et al in the JCO describing QoL impact of digital monitoring adjuvant chemotherapy. I suggest adding the reference. Your paper goes beyond that paper, but it is relevant so should add the citation.	This reference has been added where appropriate throughout the paper.	Throughout the manuscript
R3	5	The TITLE of the paper should specify that this is during adjuvant chemotherapy, by adding the word “Adjuvant” between “during” and “Chemotherapy” in the Title. This will distinguish this from the metastatic setting. This paper is an important contribution for adjuvant treatment, so ideally would be specified in the title. Otherwise that detail is buried.	Thank you for this suggestion – we have now revised the title of the paper slightly to reflect this comment and a comment from one of the other reviewers. The new title of the paper is: ‘**Real Time Remote Symptom Monitoring During Chemotherapy for Cancer: Results from eSMART, A European Multicentre Randomised Controlled Trial'**	Page 1
R3	6	Also, consider adding the word “adjuvant” in the Abstract (Objectives and Participants).	Thank you – the word ‘Adjuvant’ has been added to details in ‘objectives’ and ‘participants’ in the Abstract.	Page 2
R3	7	Introduction page 4, line 45: Suggest to delete the sentence “However, much of the evidence to date is of low quality…” This is not necessary and also is not accurate, and why insult your colleagues :-)	Thank you for this comment and apologies for any unintentional offence caused. This sentence has now been reworded.	Page 3

Rev	Point	Comment	Amendment to Paper	Page / Table / Supp File Number
R3	8	Introduction page 4, line 13: Add detail that this is during adjuvant therapy	Thank you for this comment. This has been added the Introduction section	Pages 3-4
R3	9	Box 1: Suggest to abbreviate in the text or move box to Supplement.	Box 1 removed and information incorporated in text on page 3-4 Settings and Patients section.	Pages 3-4
R3	10	Methods, Intervention, page 8, line 3: Please provide some specific details of the alert algorithm. How was it selected, and who determined it? Has it been used prior (if so please add citation). What does “clinically appropriate” mean?	Thank you for this comment – it is of a similar theme to comments from other reviewers. Changes have been made in various sections within the manuscript to provide more detail about the intervention to address those previous points and this comment too. Details of how the development of the alert algorithm and symptom specific protocols are given in the section on the study intervention. The term clinically appropriate has been taken out.	Pages 4-5 Figures 1 and 2
R3	11	Results page 8, line 15: Please provide specific details of the “evidence-based clinical decision support” system. Is there a prior publication? If so please cite it. Please explain who developed it and what it is based on.	Details around the development of the evidence-based clinical decision support has been included in the Intervention section. An additional reference providing further developmental information has been included and a PDF of the overview of the protocol for the management of nausea and vomiting has been included.	Page 4 Figure 2
R3	12	Lack of difference in hospital visits is not surprising as this is a rare event in this population. Consider adding to Limitations discussion that this result is not surprising.	This has been changed in the Discussion section.	Page 11
R3	13	I think it would be helpful to provide some more details about the intervention performance – i.e., what was happening in the clinics to drive the outcome. These might be helpful to have in the paper for any clinicians or health systems that would like to use a PRO system in the future. For example:	Additional information has been provided in relation to the patient and clinician adherence to the intervention, number of daily reports completed, number of alerts generated and responses.	Page 4; 6; 9 - 10

Rev	Point	Comment	Amendment to Paper	Page / Table / Supp File Number
R3	13a	Number of PRO self-reports by patients: - How many self-reports were completed in total among all patients. - What was the mean and median number of PRO-self reports? - What proportion of patients self-reported never, once, twice, three time, four times…. 10 times…. 20 times, etc.	Alerts were generated to clinicians via the evidence-based clinical algorithms. The frequency of alerts was dependent upon this algorithm. Further detail explaining this component of the intervention has been added to the Methods section under The Intervention sub-heading. Also, to further address this comment, we have added some additional information on the number of daily symptom questionnaires completed over the trial and the number of red and amber alerts generated for the intervention groups as a whole in the Results section under the Patient and Clinician Adherence to Intervention sub-section	Pages 4;9;
R3	13b	Alerts: - What % of PRO self-reports triggered an alert? - Please report the % for each of the individual PROs in the questionnaire (Supplement is fine). - How often did a clinician respond to the alert?	Alerts were generated to clinicians via the evidence-based clinical algorithms. The frequency of alerts was dependent upon this algorithm. Further detail explaining this component of the intervention has been added to the Methods section under The Intervention sub-heading. Also, to further address this comment, we have added some additional information on the number of daily symptom questionnaires completed over the trial and the number of red and amber alerts generated for the intervention groups as a whole in the Results section under the Patient and Clinician Adherence to the Intervention sub-section.	Pages 4;9

Rev	Point	Comment	Amendment to Paper	Page / Table / Supp File Number
R3	14	Writing: The paper is a bit wordy with some redundancy. Maybe consider editing to cut down the length, and then would have room to add some more description of the PRO intervention performance?	Thank you for this feedback - editorial changes have been made throughout the manuscript to remove redundant words and phraseology and reduce the word count. (See details below.) We have included more information on the intervention performance throughout.	Throughout document
R4 (sub-editor)	1	First, the paper remains too long and overly wordy, which makes it difficult to read. Please shorten the title (perhaps "Real Time Remote Symptom Monitoring During Chemotherapy for Cancer: eSMART, A European Multicentre Randomised Controlled Trial"), shorten the abstract to no longer than 500 words, and shorten the manuscript to longer than 5000 words. Most biomedical journal articles are 3000-3500 words. Getting to 5000 should be quite manageable and will make the paper more accessible to a broader readership.	Thank you for your comments. We have changed the title as requested. We have also cut our word count. Our Abstract is now 510 words. The word count up to the Acknowledgement section is now 5282 words.	1

Rev	Point	Comment	Amendment to Paper	Page / Table / Supp File Number
R4	2	Second, we remain confused how the adjusted mean difference between the groups was determined to be 0.15, but this is translated into an effect size of 0.5. This seems to be an overly optimistic interpretation of the difference between the two arms, but perhaps there is a misunderstanding. Most readers will see this difference as marginal. Even if this point holds up and can be clearly explained, the paper needs to be far more cautious in its interpretation. Call ASyMS the new gold standard for patient care is inappropriate, as is actively advocating for its use. The paper should present the results of the study - let the data speak for themselves.	There may be confusion of the absolute effect size and Cohen's D effect size. We have added text to explain this. The absolute effect size was 0.15 which when converted to a general unitless Cohen's D effect size is 0.15 / 0.3 = 0.5 which is considered a 'medium' effect size and so can be compared to other outcome measures. The absolute effect size is exactly what Ruland et al found in their trial so we are consistent with one of the few RCTs using this outcome. The size of the mean 0.15 may appear to be low but the population are undertaking curative initial first-line chemotherapy and many have low symptoms when compared to more advanced cancer patients seen in other studies. We have modified the text on ASyMS being the 'new gold standard' accordingly and ensured that any statements made related to this point are not only supported by the results of eSMART but also similar studies in this field.	2, 7; 8, 10; 12 - 13
R4	3	Third, the new section on "Adherence to the intervention" is useful, although the first paragraph and a half of the section should be moved to the Methods. One remaining unanswered questions: how often did clinicians initiate new therapy in response to Amber and Red Alert DCTAQs? Seems they had 8 hours to answer the former, 30 minutes for the latter. What was their adherence? I realize it says that clinicians worked through an evidence-based decision support system - but did Amber and Red alerts consistently lead to changes made to the patients' treatment plans?	This section on Adherence has been moved to methods. We have also included information on both patient and clinician adherence to the intervention and information on the actions taken by clinicians in response to alerts	6; 9;

Rev	Point	Comment	Amendment to Paper	Page / Table / Supp File Number
R4	4	Fourth, related to this point - the authors do not quite address a topic we raised in the original decision letter. Whether the marginal improvement in MSAS was less about clinician remote monitoring, and more about patients having more autonomy in their symptom management, with the ability to more readily report issues and speak to clinicians (even if changes to treatment are not made).	In the Discussion section we have provided top level information from interviews with patients and clinicians using ASyMS on what elements of the intervention they found most impactful which provides insights on what components of the intervention impacted the most on the primary and secondary outcomes. Forthcoming publications will report on patient and clinician experiences of the intervention in more detail.	9 – 10
R4	5	Finally, please pay close attention to BMJ submission requirements. For instance, citations should be inserted as superscript numbers (not embedded in the text) and numbered in the reference section.	All citations have now been inserted as superscript numbers throughout	
R4	6	When you return your revised manuscript, please note that The BMJ requires an ORCID ID for corresponding authors of all research articles. If you do not have an ORCID ID, registration is free and takes a matter of seconds.	The ORCID of Roma Maguire, the corresponding author, is on the ScholarOne system. Please advise if our understanding is incorrect.	
End of Comments				