22-Apr-2021
BMJ-2021-065142
Real Time Remote Symptom Monitoring Reduces Patient Reported Symptom Burden During Chemotherapy Treatment: Results from A European Multicentre Randomised Controlled Trial (eSMART - electronic Symptom management using the Advanced Symptom Management System (ASyMS) remote technology for patients with cancer)

Dear Prof. Maguire,

Thank you for sending us your paper, manuscript #BMJ-2021-065142 entitled "Real Time Remote Symptom Monitoring Reduces Patient Reported Symptom Burden During Chemotherapy Treatment: Results from A European Multicentre Randomised Controlled Trial". We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

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Yours sincerely,

Joseph S Ross MD MHS
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Report from The BMJ’s manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee present for the entire meeting: Helen Macdonald (chair), Jamie Kirkham (statistician), John Fletcher, Elizabeth Loder, David Ludwig, Joseph Ross, Tiago Villanueva, Wim Weber, Di Wang

Decision: Put points (revise and reconsider)

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below. Please also respond to these additional comments by the committee, summarized below. In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Editor's summary:
Prospectively registered RCT conducted at 12 cancer centres across Austria, Greece, Norway, Republic of Ireland and United Kingdom. 829 patients with non-metastatic breast cancer, colorectal cancer, or Hodgkin's Disease (HD), or non- Hodgkin's lymphoma (NHL) receiving first-line chemotherapy treatment or receiving chemotherapy treatment for the first time in the last five years were randomized to remote monitoring and management of chemotherapy-related side-effects via the mobile phone based Advanced Symptom Management System (ASyMS) or standard care to evaluate its effect on patients' perceived symptom burden. Main outcome measure was the change in symptom burden scores from the Memorial Symptom Assessment Scale (MSAS). Essentially, for the intervention group, symptom burden remained at pre-chemotherapy treatment levels, while the control group reported an immediate increase in total symptom burden from cycle 1 onwards - the adjusted mixed model estimated a least squares mean difference of -0.15. 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. 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.

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?), how often did it trigger alerts to their clinicians, what changes were made in response – I think it's critical that this information get reported. 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.

The tables need work (for instance, it is unclear why tables 1 + 2 and 4+5 were separated out when they should be combined) and nowhere do they comment on missing data or the number of individuals completing the PROMs. 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. In summary, very important topic, but the paper needs a lot of work, and its unclear whether this is a clinically significant difference.

To be clear, it does not need to be a difference that is clinically significant to be publishable in the BMJ. We would prefer a frank discussion of the intervention's benefits. A large number of RCTs have found that remote symptom monitoring are not effective for disease management (as but one example in heart failure: https://www.nejm.org/doi/full/10.1056/nejmoa1010029). No shame in testing interventions to see if they work.

Statistical editor's comments:
- 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.
- 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.
- Absolute differences should be reported for all primary and secondary endpoints, not just p values.

- More explanation of the repeated measures analysis approach would be valuable, including why actual SDs were smaller than anticipated.
- 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).
- There is also a statement that states 'No statistically significant differences were found in health systems and information needs.' This needs quantifying.
- AEs could also be better reported - in a table perhaps.
- Abstract also needs work - unclear what outcome the first result relates to.

Other Editors' comments:
- Very concerned about whether these differences are clinically-meaningful.
- Registry is not up to date, still listed as recruiting.
- Anticipated enrollment is 1100, not the 830 that were enrolled.
- 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?
- Why were 70% of patients being treated for breast cancer? What does that mean for generalizability?
- 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?
- 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.
- 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?

** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:
• Are the questions the paper addresses relevant and important to patients and/or carers?
Yes absolutely – symptom management and the side effects of intravenous chemo can be debilitating and are a worry when you don’t know how you might be affected. Knowing that you can report your symptoms as you feel them and know that within a certain time frame that your clinician will be viewing them will give reassurance to patients. Also by doing an electronic submission means that the patient doesn’t feel like they are ‘wasting’ their clinical teams time, or think that the symptoms isn’t important so it doesn’t need to be flagged.

• Are there topics or issues that are missing, or need to be highlighted more?
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. 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.

• Is the treatment or intervention suggested or guidance given something which patients/carers can readily take up? or does it present challenges?
I think if this was rolled out there would be a high take up of it as long as the patients

• Are the outcomes described/measured in the study important to patients/carers? Are there others that should have been considered?
Yes absolutely – symptoms management and the impact of chemo on life is a massive part of treatment and is often the area where patients feel the worst and don't necessarily get the support they want, because of time restraints and the belief of 'wasting time' etc.

• 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 help securely and no one can access it other than their clinical team.

• Do you think the level of patient/carer involvement in the article study could have been improved? If there was none do you have ideas on how they might have done so?
No

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Job Title: Naturopath

Institution: n/a

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Reviewer: 2

Recommendation:

Comments:
This manuscript describes a large, international, randomised control trial of remote symptom monitoring during chemotherapy given with curative intent for breast, colorectal cancers, Hodgkin's and non-Hodgkin's lymphomas. The authors are to be congratulated on performing successfully a large, complex international trial which provides clear information on the benefits of remote symptom monitoring using mobile devices. The manuscript is well written and shows a number of benefits for patients from remote monitoring. It is a valuable contribution to the scientific literature and the finding will influence clinical care.

Below are my comments aimed to clarify some points and improve the manuscript. I have first provided some major comments to be addressed which would likely require additional data, followed by comments on the text sections with references to the CONSORT requirements.

Major comments:

1.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.
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.

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).

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.

Other comments:
Title: is too long and could be reduced with the extended definition of eSMART and/or ASyMS provided in the abstract of the manuscript.

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).

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.

Methods Section:
page 4: Exact dates of study start and end usually are required to be provided rather than years.
Page 5: Why did the authors exclude patients who received weekly chemotherapy?

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 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.

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.

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.

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.

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.

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.

Registration (CONSORT item 19): both registration number and name of the trial registry are provided. Protocol (CONSORT item 24): Full protocol is attached to the publication and it has been previously published with a reference provided. Funding (CONSORT item 25): Sources of funding and other support are acknowledged with all the funders.

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.

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.

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 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.

Figure 2 should specify the range of scores on MSAS as above.
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.

Results, page 9, line 54, WLQ questionnaire results: The way this paragraph is structured leads to over-interpretation. The message is that there were no between-group differences and trends perhaps should not be discussed in detail. Suggest to re-phrase.

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.

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.

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.

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.

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".

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.

Page 11, line 49: Please state clearly that work limitations were not different between the two groups. Trends should not be reported.

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".

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.

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.

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Institution: University of Leeds

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Reviewer: 3

Recommendation:

Comments:
This multicenter RCT assesses the impact of electronic symptom monitoring during adjuvant chemotherapy on a host of patient-reports metrics including average symptom score. This is a potentially impactful study that adds to the growing literature on clinical benefits of electronic symptom monitoring during routine cancer care. The authors should be congratulated for completing this study, especially for enrolling patients right at the beginning of treatment at multiple centers, this is an accomplishment. Several comments are provided below in the spirit of improving the clarity and interpretability of the paper:

1. Clinical meaningfulness of the results. The authors followed the protocol-specified analysis plan. The a priori analysis is based on a comparison of means, and the authors conducted this analysis clearly. However, to a clinical audience interested in understanding the practical magnitude of benefit of the PRO intervention, differences in means might have limited meaning. Therefore, the following is recommended to be considered to provide some additional context for the audience:

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.

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.

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?

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.

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.

5. I think 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.

6. Also, consider adding the word “adjuvant” in the Abstract (Objectives and Participants).

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 :-)

8. Introduction page 4, line 13: Add detail that this is during adjuvant therapy.

9. Box 1: Suggest to abbreviate in the text or move box to Supplement.

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?

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.

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.

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:

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.

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?

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?

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Job Title: Professor of Medicine

Institution: University of North Carolina

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iii. For a case control study:OR (odds ratio) for strength of association between exposure and outcome.
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