Reviewer’s report

Title: Exploring the Efficacy of an Electronic Symptom Assessment and Self-Care Intervention to Preserve Physical Function in Individuals Receiving Neurotoxic Chemotherapy

Version: 0 Date: 10 Aug 2018

Reviewer: DL Hertz

Reviewer's report:

In this manuscript, the authors report a subgroup analysis of a prospective clinical trial of an electronic symptom assessment system (ESRA-C) used at home (intervention) vs. only in clinic (control). The study is limited to the subgroup of patients receiving neurotoxic chemotherapy. The authors find that the intervention prevented an overall decline in physical function and had some secondary prevention of CIPN, specifically in patients on high-dose treatment, and on treatment-induced depression. While these are intriguing findings, I have several significant concerns about the study design, particularly the patient selection for this subgroup analysis, and the baseline data. I also disagree that their primary findings, a modest difference in the physical deterioration between the groups, support their conclusion that this tool preserves physical function. Overall, this is a well-done study with important findings that are worth publication pending major revisions to the analysis and manuscript, as described in my specific comments.

Major comments:

1) One potential concern with any tool that enhances CIPN monitoring is that it will lead to earlier and more frequent treatment disruptions. Side-effect related dose disruption and, separately, neuropathy-related dose disruption should be secondary endpoints and their rates compared between control and intervention arms. The definition of chemotherapy dose reduction (Table 1) should not include disease progression or poor response as those are not side effect related and are not relevant to the intervention. Lines 378-380 mention this as a limitation but it's really a relevant outcome that is critical in understanding the benefits and harms of more intensive CIPN monitoring. The argument can be made that these dose disruptions are appropriate and are themselves evidence of a benefit, not a harm, but this issue must be directly addressed.
2) Looking at table 2, the T3/T4 difference in physical function, the primary endpoint, between the two groups is only 2.7 points. This is less than the pre-specified threshold for clinical relevance (5 points). The abstract results should include the actual scores for physical function in each group so a reader can judge for themselves the clinical relevance of this finding. I disagree that this finding supports the first sentence of your discussion (line 256) that "ESRA-C preserved physical function" (repeated in your abstract conclusion line 51) or conclusion (line 385) that "ESRA-C result in greater physical function preservation."

3) Leaving aside the modeling, essentially the main finding of the primary analysis (Table 2) is that the difference in the intervention group (3.0 point reduction in physical function) is statistically significantly smaller than the decrease in the control group (8.5 points). However, 2.8 points of that difference is due to differences at baseline. One would expect the baseline physical function to be similar between the two groups in a randomized trial. Is this baseline difference statistically significant, and if so, is there any explanation for this? Looking at the baseline scores in table 2, for every reported measure the control group is "better" at baseline (higher physical function, less neuropathy, less pain, less depression, less fatigue, less insomnia), biasing the results toward finding that the intervention prevented worsening for all of these measures. This strongly suggests that there's an issue either with the lack of study blinding, both of the patients and presumably of the clinicians who instructed the patient of how to use the tool to complete the assessments at baseline, or with decisions that were made when filtering out patients to be included in this analysis (See comment 6).

4) Line 165-175: Please define more clearly what features were available to only the intervention group and which to the control group also. Did the control group also receive the self-care messages? Did they also have access to symptom graphs? The way this is described it seems like the only difference between the group is that the intervention group could use the tool at home. It's critical to understand what variables were different between intervention and control to understand exactly what was being tested in this study.
Minor comments:

5) Line 106: It's not obvious how patient self-report and patient-doctor communication will preserve physical function. Is the implication that this tool will detect CIPN earlier, causing more treatment disruptions, and preservation of physical symptoms? That should be stated more clearly as that may or may not be seen as a positive end-result of use of this tool (related to comment 1). I recognize there is evidence that clinical use of PRO generally has been shown to preserve treatment and improve overall survival (e.g. Basch JAMA) but that seems to be due to earlier recognition of symptoms that are manageable by effective supportive care. This is not currently the case for peripheral neuropathy; earlier detection of CIPN will primarily lead to treatment disruption.

6) Line 122: Please specify what is meant by "all study-related activities." It's important to know who was filtered out of this analysis to determine whether this process was appropriate or could have introduced any bias. A CONSORT diagram of patient flow from enrollment into this analysis would be very helpful, perhaps as a supplementary figure (with reference at line 216). In the CONSORT checklist this is listed as "N/A Secondary Analysis," but this is particularly important in a secondary analysis when only a subset of the primary cohort is included, particularly in this case where there seems to be some bias at baseline in the outcome measures.

7) Line 170: Please provide more detail regarding #2: how the symptom can be managed. There are not effective means of treating peripheral neuropathy, so what was recommended? This also relates to the paragraph starting at line 291, and essentially to the entire objective of this project. If there's no way to treat or prevent neuropathy, aside from disrupting treatment, how would you expect this intervention to prevent severe CIPN?

8) Line 188: If I understand it correctly, the power calculation does not represent the primary analysis and is therefore not relevant. The study had 80% power to detect an absolute difference of 5 points between what? Is this a five point drop from baseline to T2 (or T3/T4) in a single group? Is this a 5-point difference in the difference from baseline to T2 (or T3/4) in the intervention group compared with the control group? The primary statistical analysis plan seems to have been to model the difference in the
change in physical function from baseline to T2 (or T3/T4) between the groups, but that's not what was used to estimate power. I would recommend not including a power analysis as this was a secondary analysis with a fixed cohort size that was going to be conducted regardless of a power calculation.

9) Line 190: It seems odd, in a study focused on patients on neurotoxic chemotherapy, to choose a general physical functioning scale as the primary endpoint instead of the neuropathy-specific scale (CIPN20) that was also available. Was this decision made prior to the analysis, as suggested within the manuscript? If so, please provide justification as it's important to know this to determine whether to consider these results confirmatory or more hypothesis-generating.

10) Table 1: Please describe what is meant by "cumulative dose category," to what "risk" refers, and how these risk categories were defined in the methods. I'm not aware of any established risk categorization for neuropathy, like there is for emetogenicity. In Table 2 the terms "high dose" are used in subgroup analyses of CIPN20 scores. Is this the same categorization? If so, please specify what was considered "high dose" and whether these categorizations were defined prior to analysis.

11) Lines 367-369: The data in Table 3 suggests that very few patients in the intervention group triggered any of the self-care messages. If it's not these messages that are causing the differences in outcomes between intervention and control, what could be causing the difference? Again, it was unclear exactly what the differences were in the intervention and control arm and there is concern about the lack of blinding, given the subjective patient-reported outcomes and their bias at baseline.

12) Line 306-308: Please reword for clarity or remove this sentence. It's not appropriate to state that patients were "experiencing more severe CIPN symptoms" just based on their high cumulative doses when their actual CIPN data is available.

13) Lines 311-333: While this is interesting commentary, I'm not sure it is sufficiently relevant to this study to be included in this discussion. These sentences describe limitations to the CIPN20 that are mostly relevant to its use in the clinic. This study specifically attempted to demonstrate the benefit of using an electronic screening tool outside of clinic, so neither the complexity of hand scoring nor the length of the assessment are relevant issues. The PRO-CTCAE does not overcome either of the
other two limitations, lack of cutoff scores and content validity, as noted in lines 330-333.

14) Line 356: It's unclear how one of the implications from this study is to use PRO-CTCAE to screen for CIPN since this was not included in this study in any way.

Formatting:

15) Table 1: This table is referred to as "baseline characteristics" but includes outcomes that are not known at baseline (i.e. cumulative dose, chemotherapy dose reduction). Either move these out of the baseline characteristics or change the title of the table.

16) Table 3: I recommend reformatting this table. In the first column you should have the outcome/cutpoint as the row headers. The next three columns should be T1, T2, and T3/4. In each of those cells you should put the frequency (%). It's not a major difference, but there's no reason for the extra rows and columns that are currently included.

17) Figures: Please informatively label Y-axis of all figures with information as to which outcome/scale is being displayed and indicate which direction is worsening of that outcome.

Are the methods appropriate and well described?  
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?  
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?  
If not, please explain in your comments to the authors.

No
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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