Author’s response to reviews

Title: Feasibility of a Combined Aerobic and Cognitive Training Intervention on Cognitive Function in Cancer Survivors: A Pilot Investigation

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Author’s response to reviews:

On behalf of the authors who contributed to this investigation, I would like to express my thanks and gratitude for the editor for the constructive feedback on improvement of this manuscript. We have responded to all comments and have completed a more thorough revision that should better reflect the suggestions and comments, thereby improving the quality of the manuscript.

Gratefully,

Dr. Brent M. Peterson

*In the abstract Aim should be used rather than purpose and put at the end of the background as a full sentence (not a separate section). The abstract contains p-values which should be removed as they are of little help in an underpowered study. They could be replaced with confidence intervals for the main results.
- This has been corrected as suggested.

*The title contains 'effect' which would be better replaced with 'feasibility'. It is not recommended that pilot studies report between group comparisons, just within group. It is better to be looking for trends descriptively and to use confidence intervals to show imprecision of estimates with such small numbers.

- This has been corrected as suggested. The word "effects" in the title has been replaced with "feasibility." All mentions of Kruskall Wallace global analyses have been removed and confidence intervals have been added to the abstract and results section.

*Page 4, Methods - please move the first sentence to results and the second to a new sample size section before statistical analysis.

- This has been corrected as suggested.

*Page 5 please order inclusion/exclusion criteria and participants and settings as per CONSORT extension guideline. This is the least clear section. What was screened for - a little more explanation is needed.

- This has been corrected as suggested. The inclusion/exclusion criteria section has also been reworked to reflect the suggestions. In now reads as, “Twenty-eight male and female participants undergoing treatment for cancer were eligible to participate in this study. Participant eligibility was initially screened by front office staff prior to his or her arrival at UNCCRI for the first physical assessment. Patients were, initially, be younger than 69 years of age, were physically inactive (aerobic exercise < 2 times a week), and had not been using any cognitive training software within the 8 weeks prior to them coming to UNCCRI for investigators to speak with them further about study participation. Following initial screening and agreement to participate participants then completed the standard UNCCRI comprehensive physiological assessment detailed in subsequent paragraphs. Following the completion of initial UNCCRI physical assessments, investigators then employed in-person recruitment strategies. It was during these follow-up discussions that investigators would ask potential participants a series of questions that were of greater depth than during the initial round of questions. Participants were excluded from the study if they reported any of the following, 1) a history of psychiatric disease, 2) any past history of neurological disease, 3) past or present alcohol or substance abuse, 4) difficulty with
mobility, 5) auditory dysfunction, or 6) non-corrected visual issues. Participants that qualified were then asked for their interest to participate. Those that declined to participate did so verbally, and immediately began the standard UNCCRI exercise programming. The University of Northern Colorado Institutional Review Board approved [573297-2] all procedures and written informed consent forms were signed by all subjects.”

*Page 8 is confusing. Please put relevant sentences under the relevant heading eg lines 58-60 under AER, page 8 lines 4-9 under COG. Please point out that the flexible active control group is referred to as COG on page 8.

-This has been corrected as suggested. This investigators have elaborated on each of the paragraphs describing intervention arms to more efficiently differentiate between the treatments.

*Page 9 why does the flowchart not contain four arms? This is confusing. Please amend to show the four arms into which people are randomized.

- This has been corrected and figure 1 has been updated.

*Please explain the process in more detail in a section headed Randomization.

- This has been given added explanation and emphasis as recommended. It now reads as follows.

Randomization

Randomization was completed a priori using PROC PLAN (SAS 9.3, Cary, NC), a statistical tool that generates a randomized numerical listing of intervention groups. For example, the AER + COG group was numerically listed as group 1, the AER group was listed as group 2, the CON group was listed as group 3, and the COG group was listed as group 4. As participants were pre-screened and qualified for the study they were then assigned to the next available intervention group on the list. All participants in each group were unaware of the number of different intervention groups. Throughout the study, however, 5 subjects presented with specific physician recommendations that required placement into a group other than the random selection, thereby
nullifying complete random assignment. The PI enrolled participants and assigned participants based on the next group that appeared on the list.

*Please add a sample size section giving some rational for the sample size chosen and move any relevant text to this section.

- This has been corrected as suggested. It now reads as follows.

Sample Size

This investigation is the result of doctoral work completed by the PI while at the University of Northern Colorado. Sample size was originally intended to exceed 40 participants (G *Power, ver. 3.0.10), yet as the limitations will describe in the upcoming paragraphs, multiple factors influenced the resultant N of 28. Throughout the process, the challenge of 1) enrolling willing and eligible participants into the study, 2) attendance to ongoing medical concerns of participants, and 3) the impacts of various occurrences of treatment-related side effects posed the greatest detriments to full completion of 40 participants. As a result, data collection took longer than anticipated. When the time limit for the study was reached data collection ceased.

*There is a cautionary caveat about small numbers and the use of p-values but still their use is given too much emphasis in the text. Please use CIs more in presenting the results.

- This section has been amended to reduce the emphasis on p-values utilized in the text as requested. It now reads as follows.

Twenty-eight cancer patients (58 ± 8 yrs.; 6 males, 22 females) participated in the study. Pre-to-post means and SD, confidence intervals, and pre-to-post percentage changes are reported in Tables 5, 6. Subjects in the CON group showed pre-to-post improvements in verbal fluidity scores only. It was hypothesized that cognitive training alone and aerobic training alone would each, independently, improve cognitive function. While subjects in the AER group did show improvements, the COG group showed no improvements in cognitive function. The AER group showed pre-to-post improvements using Logical Memory I (95% CI [-4, -.9]), Logical Memory
II (95% CI [-4, -.3]), Block Design (95% CI [-3, -.2]), and Letter Number Sequencing tests (95% CI [-2, -.2]).