Author's response to reviews

Title: The effects on depression of Internet-administered behavioural activation and physical exercise with treatment rationale and relapse prevention: study protocol for a randomised controlled trial

Authors:

Per Carlbring (per@carlbring.se)
Philip Lindner (phiplindner88@gmail.com)
Christopher Martell (christophermartellphd@gmail.com)
Peter Hassmén (peter.hassmen@psy.umu.se)
Lars Forsberg (lars.forsberg.3@ki.se)
Lars Ström (lars.strom@psy.umu.se)
Gerhard Andersson (gerhard.andersson@liu.se)

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Author's response to reviews: see over
Dear Editor,

Please find attached our responses to the constructive comments by our appointed reviewer, Professor Dr. John Norrie. We agree that the suggested revisions have improved the clarity and overall quality of the article.

In addition to the comments we received, we have made minor changes in wording to improve clarity, as well as correcting typos. Since first submission, we have decided to exclude the motivational interviewing component of the trial, for practical and scientific reasons. Both the physical exercise and BA groups will now be randomized to either with or without a clear treatment rationale. Three additional instruments will also be included to increase the scientific validity of the trial. Appropriate revisions have been made to reflect these changes. Changes are tracked and marked, as requested.

We thank you in advance for your consideration of this revised manuscript for publication in *Trials*.

With kind regards,

Professor Dr. Per Carlbring
Department of Psychology, Stockholm University, Sweden

per@carlbring.se
1a. What is the difference between general behavioural activation and physical exercise, both described as types of activation? What is the theoretical underpinning that would explain how these interventions -will achieve beneficial effects on the chosen primary outcome?

We thank the reviewer for bringing to our attention the need to clarify this. We have added several lines in the Introduction (section 1) discussing this matter:

“In this therapeutic context, physical exercise can be considered a focused form of behavioural activation [6] in the respect that both interventions require the client to schedule and perform activities. A recent innovative randomised controlled trial comparing aerobic exercise to low-intensity stretching—both treatment arms having equal levels of activity frequency and social interaction—found no between-group difference in antidepressant effect [7]. An explanation for this result could be that it is the common activation component that causes the antidepressant effect, rather than the physical exercise per se. At present it is unknown whether any antidepressant effects of behavioural activation and physical exercise are treatment-specific or due to the common activation factor. Using an advanced trial design, the study herein described will be able to evaluate the antidepressant effects of both the respective treatments in themselves, and compare the two.”

b. Why split the two active groups into 4 - BA with and without treatment rationale, and physical exercise with or without motivational interviewing? Is the without treatment rationale really an option - and why would you want to exclude it e.g. is it just on grounds of cost and speed of delivering the intervention?

We recognize that this is an area in need of clarification. In the Introduction (section 1), we have added the following lines:

“Explaining the BA treatment rationale to patients is widely considered an early step in treatment [6], yet the component-specific effect of providing this rational has not yet been the subject of research. Acknowledging the well-known effect on outcome in cognitive behavioural therapy of client acceptance of treatment rationale [10], this study will be able to distinguish the effect of providing a clear and extensive treatment rationale in BA therapy.”

Reflecting the change in interventions (the exclusion of motivational interviewing), we have also added the following passage in the Introduction:

“Indeed, the specific mechanism by which physical exercise has an effect on depression—if any—is still unknown. As is the case with BA therapy, no previous research has studied the unique, component-specific effect of providing a clear treatment rationale. Providing this rationale may increase the patient’s motivation to exercise, which in itself may give a direct placebo-type antidepressant effect and/or indirectly reduced depressive symptoms following increased physical activity (which can be measured). This trial will be the first to study the component-specific effect of providing a clear treatment rationale in physical exercise therapy for depression.”

The specifics of “without treatment rationale” are described in section 2.3.3-4.
In this trial, we are interested to study the separate effect of treatment rationale in BA and physical exercise therapy. The results will have an impact on how the treatment rationale component is viewed and used in these kinds of interventions.

c. Likewise it would seem that given the difficulty across all sorts of subsets (e.g. obesity) of getting people to exercise, why go without the motivational interviewing? Why not give the BA and the PE in their best possible form and make it a 3 arm trial? If one proves superior then you can investigate in a subsequent trial fine tuning the delivery of that intervention?

This is an interesting discussion, albeit not one we feel is necessary to include in the paper. It is our belief that the research questions addressed in this trial warrant investigation and that all the included research questions can be addressed in a single, large trial.

2. There was very little on safety reporting - this seems an omission. Yes, the design tries to exclude the severely depressed or those identified at screening as being suicidal, and the interventions may be seen as low risk - but nonetheless safety should be addressed.

We thank the reviewer for bringing this matter to our attention. We have the highest possible ethical ambition and do not want any reader to think otherwise. We have now included a novel, separate section (2.6 Ethics) addressing our ethical concerns.

3. For example it is not clear that the combination of internet based screening relying only on patient recorded responses and then a telephone interview for diagnosis seemingly conducted by masters level trainee psychologists is going to infallibly identify all those at high risk of harm?

Please see (2) above.

4. And there does not seem to be any independent oversight of the trial specified - usually there would be independent Trial Steering Committee and possibly an independent Data Monitoring Committee, getting regular updates on trial progress and any safety issues as mentioned above?

As the reviewer correctly concludes, this trial features no independent oversight committee. There are several reasons for this, which we do not feel are necessary to discuss in the paper. With the small exception of the commercial interest of one of the authors (CM), described in the Competing interest section of the paper, this study lacks commercial ties. Also, neither theory nor past empirical research suggests any adverse impact in need of independent monitoring. The trial was awarded ethical approval without an independent monitoring committee.

If the editor wishes, we would be happy to provide this rationale in the paper.
5a. How are the control group subjects going to be used in the analysis after they are re-randomised?

Please see (5c) below.

b. How will the second randomisation to relapse prevention deal with the time lag of 12 weeks for the control group

Please see (5c) below.

c. Are the comparisons of interest BA (1+2) vs. control (5); and PE (3+4) vs. control (5); and BA (1+2) vs. PE (3+4); and BA(1) vs BA(2); and PE(3) vs PE(4)?

We acknowledge that this was unclear. In section 2.5, we have added a paragraph on the planned comparisons:

“The study design will allow for multiple comparisons: the two physical exercise groups (separately and together) will be compared to controls, as will the two BA groups (separately and together). In all other analyses, the groups in question will include those from the control group later randomised to interventions, this to increase the statistical power. The two physical exercise groups will be contrasted with the two BA groups. Further, the physical exercise group with treatment rationale (group 1) will be contrasted with the group without (group 2), and the BA group with treatment rationale (group 3) will be contrasted with the BA group without (group 4). Finally, the four groups receiving relapse prevention will be contrasted with the four groups that do not. At the 12 and 24 month follow-ups, within-group comparisons will be made with previous results.”

d. If so, what adjustments are going to made for multiple comparisons? It wasn't clear whether the sample size calculation took the multiple number of comparisons into account?

We acknowledge that these aspects were unclear and have made revisions. The sample size calculation is based on the primary analysis and takes the multiple number of comparisons into account by a bonferroni-adjustment. We have added a sentence in section 2.5 addressing this issue.

The sample size is calculated to detect a moderate difference (0.5 standardized units) in the primary outcome PHQ-9 between the control and each of the four treatment groups at the 12 weeks follow up. A total of 91 subjects in each group are required to detect this difference with 80% power and overall significance at 5% significance level (bonferroni-adjusted, i.e. significance level = 0.0125 (0.05/4) in each comparison), two tailed. Since we anticipate that patients will be lost to follow up, the recruitment goal is therefore determined to a total of 500 subjects (100 in each group). Revisions to section 2.2 in the paper have been made.

6. How will pharmacotherapy be measured and possibly adjusted for as a confounder?
Parallel pharmacotherapy constitutes a threat to the validity of the trial and will naturally be adequately assessed. We have made an addition in section 2.2 explaining our procedure (additions in italics).

“Use of psychoactive medication is not grounds for non-inclusion if the dosage has been stable for the past three months and will continue to be stable during the intervention period. Any changes in medication during the study period will be noted along with the other measurements at treatment completion and the 12 and 24 month follow-ups. If the proportion of patients who use pharmacotherapy differs between the treatment groups we will use pharmacotherapy metrics as a factor in the mixed model analysis to adjust for a possible confounder effect when treatment effects are studied.”

Although we do not consider it necessary to include in the paper, we would also like to add that any changes in medication are likely to be addressed in the client-therapist communication, as is our clinical experience.

7. The protocol is clear on the 'intentional' missing data generated by the 33% visits schedule per month - but what of the non-design missing data due to loss to follow up, participant withdrawal, and so on - obviously the authors will develop a comprehensive Statistical Analysis Plan (SAP) to govern the analyses – how they intend to deal with the missing data should be a key part of that specification.

We have clarified our procedure described in section 2.5, which now reads (additions in italics):

“To find potential predictors of treatment outcomes (including treatment adherence and drop-out), logistic regression analysis on background variables will be performed (see [43]).

Since all questionnaire data will be supplied directly by the participants through the online interface, there is no risk of data loss or data distortion along the way. Data will be stored encrypted and in unidentifiable form (using participant-numbers). Standard missing data analysis will determine if unexpected missing data due to participant drop-out is random or not.”

8. It is not specified how intense / how long the exercise programmes for the individuals will be? What is the likely average and range?

We acknowledge that this detail was not clearly specified and have clarified it accordingly in sections 2.3.1 and 2.3.3.