Reviewer's report

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

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Reviewer: John Norrie

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Discretionary revisions

The authors present a well written protocol on a complex set of interventions on an important area of clinical need. There are a number of issues that could benefit from clarification, as follows:

1. This is a complex design, with 4 active groups, and a waiting list control group who then get re-randomised to one of the 4 active groups after 12 weeks. There is also a second intervention of relapse prevention after the 12 weeks. The authors need to more clearly explain and justify the choice of treatments - specifically:
   a. 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?
   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?
   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?

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.
   a. 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?
   b. 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?

5. As indicated, this is a complex design, with 4 active groups, and a control group that transitions to active, and then a further randomised experiment on relapse - we need at least basic detail on the statistical analyses and what comparisons are going to be made between which groups at what time points - several issues:

a. How are the control group subjects going to be used in the analysis after they are re-randomised?

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

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)?

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?

6. How will pharmacotherapy be measured and possibly adjusted for as a confounder?

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.

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