Author's response to reviews

Title: Adding smartphone-based cognitive-behaviour therapy to pharmacotherapy for major depression (FLATT project): study protocol for a randomized controlled trial

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Editors-in-Chief

Professors Doug Altman, Curt Furberg and Jeremy Grimshaw,

TRIALS

RE: Adding smartphone-based cognitive-behaviour therapy to pharmacotherapy for major depression (FLATT project): study protocol for a randomized controlled trial

Dear Professors Altman, Furberg and Grimshaw,

We are most grateful to you and the reviewers for helpful comments on our manuscript. We have addressed all the comments from the reviewers, as indicated on the attached pages.

We hope that our revised manuscript is considered suitable for publication in Trials.

Yours sincerely,

On behalf of my co-authors,
Norio Watanabe and Toshi A. Furukawa
Adding smartphone-based cognitive-behaviour therapy to pharmacotherapy for major depression (FLATT project): study protocol for a randomized controlled trial

We are most grateful to the reviewers for helpful comments on our manuscript. We have addressed all the comments as follows.

<table>
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<tr>
<th>Comment</th>
<th>Response from the authors</th>
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<tbody>
<tr>
<td>Referee 1</td>
<td></td>
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<tr>
<td>1</td>
<td>1) Gotzsche in Lancet Psychiatry 2014 argued that ADMeds produced two important side effects that were not usually asked about; sexual difficulties and difficulties in discontinuing. FIBSER does not cover either. I recommend that questions on sexual difficulties be included; and that information be reported on the frequency with which subjects were deleted because they could not cease their first ADMed.</td>
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</table>
outcome defined as “Deviation from protocol treatment” described in the Methods section. Please note that such patients would not be excluded from our primary analyses because our ITT population would include patients for whom we “plan” to switch antidepressants and to add smartphone CBT or not. We hope that these response will prove satisfactory with the reviewer.

2 2) the power calculation is based on two meta analyses in which the majority of Ss were not on meds. All Ss in the intervention group will be on meds so perhaps the best guide as to power might come from the recent Watts et al paper on the superiority of CBT over treatment as usual. From those data 0.5 ES might still be reasonable, but according to StarD, the power of a second line of treatment, CBT or Meds, was reduced by some 40% in comparison to when the same treatment was used as the first line of treatment, and this would further erode the power of this study. To be safe I think that I would work on CBT adding less that 0.5SD to the benefit of meds.

We appreciate the reviewer’s comment, because many readers may have similar ones. We have further described our thoughts about the estimate effect size in the present study as follows among the limitations in the Discussion section: “Fourth, although the effect size of 0.5 used for calculation of sample sizes was estimated from results of the previous studies on the efficacy of computer or internet-based CBT {So, 2013 #8}{Andrews, 2010 #7}, one may think that the effect size is too optimistic because the present study focuses on patients with treatment-refractory depression. In addition, a majority of the control conditions used in trials included in previous systematic reviews {So, 2013 #8}{Andrews, 2010 #7} were waiting-list, which might have led to plausibly large effect sizes. However, our previous clinical trial comparing the efficacy of a telephone-based CBT program added to the employee assistance program with that of the latter alone showed an effect size of 0.69 {Furukawa, 2012 #36}. The smartphone-based CBT program in the
The present study was based on this telephone-based program, and we considered that the estimated effect size of 0.5 in the present study was reasonable. We hope that this response will satisfy the reviewer.

<table>
<thead>
<tr>
<th>Referee 2</th>
<th>1. First, what are the hypotheses or expected results? I regret I was not able to see any noted in the manuscript.</th>
<th>Thank you. The hypotheses has been added at the end of the Background section as follows: “We hypothesized that adding a smartphone-based CBT program to switching antidepressants could lead to more improvement in depression symptoms among patients with treatment-refractory depression than switching antidepressants alone”.</th>
</tr>
</thead>
</table>
| 2. Second, I am curious about the adequacy of the sample size in light of several factors. These include that the referenced benchmarks do not compare active treatment conditions, and thus may over-estimate the expected gains in the present trial, which compares active treatments. In addition, the sample for the present trial are potentially treatment resistant, and gains in this sample may be minimal. It would be helpful if the authors addressed these issues. | We appreciate the reviewer’s comment, because many readers may have similar ones. We have further described our thoughts about the estimate effect size in the present study as follows among the limitations in the Discussion section: “Fourth, although the effect size of 0.5 used for calculation of sample sizes was estimated from results of the previous studies on the efficacy of computer or internet-based CBT (So, 2013 #8){Andrews, 2010 #7}, one may think that the effect size is too optimistic because the present study focuses on patients with treatment-refractory depression. In addition, a majority of the control conditions used in trials included in previous systematic reviews (So, 2013 #8){Andrews, 2010 #7} were waiting-list, which might have led to plausibly large
effect sizes. However, our previous clinical trial comparing the efficacy of a telephone-based CBT program added to the employee assistance program with that of the latter alone showed an effect size of 0.69 \cite{Furukawa, 2012 #36}. The smartphone-based CBT program in the present study was based on this telephone-based program, and we considered that the estimated effect size of 0.5 in the present study was reasonable”. We hope that this response will satisfy the reviewer.