PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Strategy for treating selective serotonin reuptake inhibitor-resistant social anxiety disorder in the clinical setting: A randomised controlled trial protocol of cognitive behavioural therapy in combination with conventional treatment
AUTHORS	Yoshinaga, Naoki; Niitsu, Tomihisa; Hanaoka, Hideki; Sato, Yasunori; Ohshima, Fumiyo; Matsuki, Satoshi; Kobori, Osamu; Nakazato, Michiko; Nakagawa, Akiko; Iyo, Masaomi; Shimizu, Eiji

VERSION 1 - REVIEW

REVIEWER	Gerhard Andersson, PhD, Professor Linköping University Sweden
REVIEW RETURNED	18-Nov-2012

GENERAL COMMENTS	I read this protocol with great interest. My main concern is not the study idea, but rather selective referencing. Here are some suggestions that might be of help. 1. Intro. I do not think it is fair to say that there is limited trial based evidence for the treatment of generalized SAD. Indeed, there are numerous CBT trials in which they are included and often a majority of the participants. 2. In some places in the ms attention should be paid to language and expression, like this sentence: "less attention from the marketing"??? I wonder if they mean pharmaceutical companies or what market do they mean? 3. The intro should outline the evidence in favour of CBT as a first line treatment. This is a strange omission now. Indeed, evidence suggests that CBT has long term effects including long term effects of internet-delivered CBT (e.g., Hedman et al. 2012 JMIR), and in addition it might be worth mentioning that patients often prefer psychological treaments (even if this is more well known in the depression literature). 4. CBT program. There are now much evidence in support of internet-delivered CBT and hence there are three forms of CBT, not only individual and group-based. 5. The power calculation makes no sense. The authors state that they have found that 36 subjects per arm will be needed, but then end up with 21 in each arm. I also wonder how reliable their estimate of 30 points difference on the LSAS when two active treatments are compared. I assume this is valid it the medication arm is assumed to be largely ineffective. If so, this could be stated more clearly. Otherwise I suggest the authors add participants to at least 100, which would allow for the the detection of a smaller difference on the LSAS. There might be a writing mistake here if the authors instead mean 42 participants per arm. 6.Regarding the statistics I would appreciate if the authors state their

	expected dropout and also HOW they will impute missing data. 7. Regarding possible drawbacks I would appreciate mentioning of the potential problems with assessing "treatment resistant SAD" and also that the authors reflect on the possibility of participants having failed other treatments than SSRI, for example supportive counselling. Overall, however, this is a timely study that will fill a gap in the literature.

VERSION 1 – AUTHOR RESPONSE

Reviewer's comment 1
> Intro. I do not think it is fair to say that there is limited trial based evidence for the treatment of generalized SAD. Indeed, there are numerous CBT trials in which they are included and often a majority of the participants.

Author's comment
Thank you very much for your helpful advice. According to reviewer's comment 1, we added "First-line cognitive behavioral therapy" subsection of the "INTRODUCTION" section, and described about effectiveness of CBT.

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Reviewer's comment 2
> In some places in the ms attention should be paid to language and expression, like this sentence: "less attention from the marketing"??? I wonder if they mean pharmaceutical companies or what market do they mean?

Authors' response
Thank you for pointing this out. We revised 'less attention from the marketing' to 'less promotion from pharmaceutical companies' in the second paragraph of 'First-line cognitive behavioural therapy' subsection of the 'INTRODUCTION' section.

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Reviewer's comment 3
> The intro should outline the evidence in favour of CBT as a first line treatment. This is a strange omission now. Indeed, evidence suggests that CBT has long term effects including long term effects of internet-delivered CBT (e.g., Hedman et al. 2012 JMIR), and in addition it might be worth mentioning that patients often prefer psychological treaments (even if this is more well known in the depression literature).

Authors' response
Thank you very much for your suggestion. We revised the subsection entitled 'First-line cognitive behavioural therapy' and added a sentence describing CBT's potential advantages over pharmacotherapy. Moreover, we cited some of the studies suggested by one of the reviewers. Please also see our responses to Reviewer's comment 1.

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Reviewer's comment 4
> CBT program. There are now much evidence in support of internet-delivered CBT and hence there are three forms of CBT, not only individual and group-based.

Author's comment
Thank you very much for your helpful advice. We added internet-delivered CBT to the different formats of CBT mentioned. We also moved the sentence about the type of CBT and the effectiveness of internet CBT to the 'First-line cognitive behavioural therapy' subsection of the 'INTRODUCTION' from the 'CBT program' subsection.

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Reviewer's comment 5
> The power calculation makes no sense. The authors state that they have found that 36 subjects per arm will be needed, but then end up with 21 in each arm. I also wonder how reliable their estimate of 30 points difference on the LSAS when two active treatments are compared. I assume this is valid it the medication arm is assumed to be largely ineffective. If so, this could be stated more clearly. Otherwise I suggest the authors add participants to at least 100, which would allow for the the detection of a smaller difference on the LSAS. There might be a writing mistake here if the authors instead mean 42 participants per arm.

Authors' response
Thank you for pointing this out. We have now mentioned that the conventional treatment arm is assumed to be largely ineffective in the 'Sample size' section. Moreover, we sincerely apologize for the inaccurate description indicating that '36 subjects per arm will be needed'. We actually assumed a group difference of 30 points (SD = 30), indicating that 18 subjects per arm will be needed. Allowing for a 20% dropout rate, 21 participants are required per group, for a total of 42 patients in our study.

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Reviewer's comment 6
> Regarding the statistics I would appreciate if the authors state their expected dropout and also HOW they will impute missing data.

Authors' response
Thank you for pointing this out. We do not handle missing observations in the primary analysis, however multiple imputation method will be applied as a sensitivity analyses. Details of statistical analysis will be defined in our statistical analysis plan (SAP) until data fixation. We added this sentence in the "Statistical Analysis" section as follows.

'Statistical analysis and reporting of this trial will be conducted in accordance with CONSORT guidelines, with the primary analyses based on intent-to-treat principle without imputing missing observations. As a sensitivity analyses, multiple imputation method will be applied to examine the effect of missing data.'

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Reviewer's comment 7
> Regarding possible drawbacks I would appreciate mentioning of the potential problems with assessing "treatment resistant SAD" and also that the authors reflect on the possibility of participants having failed other treatments than SSRI, for example supportive counselling.

Author's comment

Thank you very much for your helpful advice.

1) To the best of our knowledge, there is no definition of ‘treatment resistance’, ‘medication resistance’, or ‘SSRI resistance’. To obtain a clear definition of treatment resistance (especially medication resistance) in social anxiety disorder would warrant further discussion. We focused only on ‘SSRI resistance’.
Considering only SSRI resistance, non-response and intolerance are common among treated patients. Regarding your suggestion, we supplemented the details about intolerance in the ‘Participants’ subsection as ‘……., or intolerance to SSRIs (e.g. because of drowsiness, nausea, sleep disturbances, sexual dysfunction, and appetite change)’.

2) SSRI treatment usually includes some type of non-specific psychotherapy (e.g. supportive counselling) from the general practitioner. We added a sentence to indicate this: ‘Of course, SSRI treatment usually includes some type of non-specific psychotherapy (e.g. supportive counselling) from the general practitioner.’ at the end of the ‘First-line pharmacotherapy’ subsection.