PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Does internet-based cognitive behaviour therapy reduce healthcare costs and resource use in treatment of social anxiety disorder? A cost- minimisation analysis conducted alongside a randomized controlled trial
AUTHORS	El Alaoui, Samir; Hedman, Erik; Ljótsson, Brjánn; Lindefors, Nils

VERSION 1 – REVIEW

REVIEWER	Wouter van Ballegooijen Vrije Universiteit Amsterdam, Netherlands
REVIEW RETURNED	06-May-2017

GENERAL COMMENTS	This is a well written paper that might be of high impact. Despite the intuitive idea that iCBT should be cheaper than face-to-face therapy, cost-effectiveness studies often apply limited methodology and aren't usually very convincing in my opinion. The method applied here, time-driven activity based costing, appears to be more straightforward and reliable than previous cost assessments. A point of discussion would be which costs should be included in the analysis. I'd like to invite the authors to provide more detail, e.g. in table 1. Was the training of therapists included? And what about hosting and data security? Did the therapists need new IT equipment? The more details the authors could provide, the more convincing this paper would become. A few other points: What was the treatment adherence and can it have impacted the results? Data were collected a few years after the study. To what extend was it possible to retrieve all costs? The cost-effectiveness analysis is not explained in the analysis section. Some readers may not be familiar with this type of analysis.

REVIEWER	Mario Mazzocchi Department of Statistical Sciences, University of Bologna, Italy
REVIEW RETURNED	08-May-2017

GENERAL COMMENTS	This is an interesting and well written paper, but I have some concern about the application of cost minimization analysis without accounting for uncertainty and type II error in the evaluation of effectiveness. The authors have used a conservative approach in

	looking for evidence of effectiveness, which inflates Type II error, and they have not considered this source of uncertainty when comparing cost. However, ICBT outperforms CBGT both in terms of effectiveness and minor costs, which suggests that the study conclusions are valid. However, a better effort to show the robustness of the cost estimates should be provided in my opinion. 1) I think the paper could benefit by a more appropriate discussion of this aspect in the application of CMA. See the paper by Briggs and O'Brien (reference below), where the concern is placed on the overlooking of Type II errors. Your primary step is based on non-inferiority analysis, which makes the possibility of Type II errors even larger. Briggs et al. to provide an appropriate representation of uncertainty considering cost-effectiveness or relying on a net-benefit statistic. It would be interesting to see (1) a more explicit accounting of the effectiveness study, at least the basic results, even if published elsewhere; (2) a robustness check when uncertainity is accounted for. 2) The authors indicate some standard assumption in their cost-evaluation exercise, for example "the practical capacity of each staff category was estimated to be 80% of the actual number of worked hours" or "Costs and were discounted at an annual rate of 5% and are presented in €, year 2017 values" (see also the typo in this sentence). A table showing how results and mean comparison tests change when these assumptions are changed in various direction would be relevant to show robustness of the findings. Briggs, A.H. and O'Brien, B.J. (2001) The death of cost-minimization analysis? Health Economics 10(2):pp. 179-184.

VERSION 1 – AUTHOR RESPONSE

Response to Comments from Reviewer 1
Comment 1:
I'd like to invite the authors to provide more detail, e.g. in table 1. Was the training of therapists included? And what about hosting and data security? Did the therapists need new IT equipment? The more details the authors could provide, the more convincing this paper would become.

Response:
We greatly appreciate the reviewer's efforts to carefully review the paper and the valuable suggestions offered. As suggested by the Reviewer, we have added more detail on describing the costs of care and a more detailed description of how capacity cost rates were calculated. Please refer to page 8, first paragraph, in the revised manuscript.

Comment 2:
What was the treatment adherence and can it have impacted the results?

Response:
Thank you for the comments. We have now included a report on treatment adherence in the manuscript (page 10, last paragraph). Both adherence (approximately 9 sessions/modules) and health improvements were similar across treatment conditions, In a previously published predictor study on the same sample, it was found that for both treatments, adherence was a significant predictor of outcome, where completing at least five sessions or modules predicted better outcome

(Hedman, E., Andersson, E., Ljótsson, B., Andersson, G., Andersson, E., Schalling, M., . . . Ruck, C. (2012). Clinical and genetic outcome determinants of Internet- and group-based cognitive behavior therapy for social anxiety disorder. Acta Psychiatrica Scandinavica, 126(2), 126-136. doi: 10.1111/j.1600-0447.2012.01834.x).

Comment 3:
Data were collected a few years after the study. To what extend was it possible to retrieve all costs?
Response:
Cost estimates were based on average wages from the time period. Although original data from the RCT on recorded time spent on treatment was collected, additional time studies on administrative and assessment procedures were conducted after the intervention study was completed. Therefore, difficulties in retrieving exact cost data may add to the uncertainty around cost estimates. We have added this as a limitation in the Discussion section (page 11, fourth paragraph).

Comment 4:
The cost-effectiveness analysis is not explained in the analysis section. Some readers may not be familiar with this type of analysis.

Response:
We appreciate the Reviewer's comment. We have now expanded on the explanation of the cost-minimization analysis (page 5, last paragraph) and compared the difference in use relative to four commonly used methods in health economic evaluations (cost-benefit analysis, cost-effectiveness analysis, cost-utility analysis and cost-minimization analysis).

Response to Comments from Reviewer 2
Comment 1:
I think the paper could benefit by a more appropriate discussion of this aspect in the application of CMA. See the paper by Briggs and O'Brien (reference below), where the concern is placed on the overlooking of Type II errors. Your primary step is based on non-inferiority analysis, which makes the possibility of Type II errors even larger.
Briggs et al. to provide an appropriate representation of uncertainty considering cost-effectiveness or relying on a net-benefit statistic.
It would be interesting to see (1) a more explicit accounting of the effectiveness study, at least the basic results, even if published elsewhere; (2) a robustness check when uncertainity is accounted for.

Response:
We appreciate the comments by reviewer 2 and have supplemented information as for the effectiveness study in the Introduction section (page 5, second paragraph). In regard to accounting for the uncertainty, we have used the statistical methods of cost-effectiveness, as recommended by the Reviewer, to evaluate the uncertainty around the costs and effects. This is presented in the cost-effectiveness plane in Figure 1, where ellipses illustrates the uncertainty surrounding the estimated cost-effect difference between the two treatments at difference confidence intervals. We have also included a cost-effectiveness acceptability curve (CEAC; see Fig. 2.) and, as suggested, calculated the incremental net benefit (INB) to interpret the CEAC (see Fig. 3.).

Comment 2:
The authors indicate some standard assumption in their cost-evaluation exercise, for example "the practical capacity of each staff category was estimated to be 80% of the actual number of worked

hours" or "Costs and were discounted at an annual rate of 5% and are presented in €, year 2017 values" (see also the typo in this sentence). A table showing how results and mean comparison tests change when these assumptions are changed in various direction would be relevant to show robustness of the findings.

Response:
This is an important issue. As suggested by the Reviewer, we have now included Table 2 showing how estimated costs and mean differences change when assumptions of discount rates are changed. We have also added a reference to Table 2 in the manuscript text (please see page 10, second paragraph).

VERSION 2 – REVIEW

REVIEWER	Wouter van Ballegooijen Vrije Universiteit Amsterdam, Netherlands
REVIEW RETURNED	19-Jun-2017

GENERAL COMMENTS	The manuscript has improved and I thank the authors for addressing my comments. Two of my points still stand. I invite the authors to comment on which costs should be included in the analysis. Implementing an iCBT intervention in clinical practice takes time, effort and budget. The intervention needs to be developed. There are costs for keeping the intervention hosted and protected. You have to make sure the intervention can run on the computers of the professionals. Therapists need to be trained to be able to work with the iCBT intervention. There might be other costs related to the specific infrastructure of your institution. Are these costs included in the analysis (and Table 1) and if not, why not? Hospital space costs are now explained, but these do not translate directly to the costs presented in Table 1. Cost-effectiveness analysis is not explained in the Analysis section. I am referring to this sentence in the Analysis section: 'In order to avoid biased estimation of uncertainty, we have used the statistical methods of cost-effectiveness to evaluate the joint distributions of costs and benefits.' Cost-effectiveness analysis requires several steps and decisions. Moreover, some readers may not be familiar with this type of analysis. It would add to this paper to explain how this was done and in which way it deviates from traditional cost-effectiveness analysis.

REVIEWER	Mario Mazzocchi Department of Statistical Sciences, University of Bologna (Italy)
REVIEW RETURNED	19-Jun-2017

GENERAL COMMENTS	Thanks for providing the uncertainty analysis. The authors may want to state somewhere that even if the original analysis was a "non-inferiority" one, and the results showed that the two approaches can be treated as 'equivalent', but (if I am correct) the direction of effectiveness is still pointing towards the cheaper method, so that the worry on Type II error is not crucial. I would make this discussion explicit and cite the Briggs paper I had mentioned in the previous review. Second, Table 2 shows that changing the discount rate does not

	change the direction of the cost-effectiveness, which is good. However, it would be interesting to see a similar sensitivity analysis for other assumptions, e.g. the 80% assumption ("the practical capacity of each staff category was estimated to be 80% of the actual number of worked hours"). What happens if one assumes that it is 50% or 100%?

VERSION 2 – AUTHOR RESPONSE

Response to Comments from Reviewer 1
Comment 1:
I invite the authors to comment on which costs should be included in the analysis. Implementing an iCBT intervention in clinical practice takes time, effort and budget. The intervention needs to be developed. There are costs for keeping the intervention hosted and protected. You have to make sure the intervention can run on the computers of the professionals. Therapists need to be trained to be able to work with the iCBT intervention. There might be other costs related to the specific infrastructure of your institution. Are these costs included in the analysis (and Table 1) and if not, why not?
Hospital space costs are now explained, but these do not translate directly to the costs presented in Table 1.

Response:
The costs mentioned by the reviewer is included in the cost rates (minute cost) for each personnel category. The costs in Table 1 therefore include these allocated costs. I.e., the minute cost for a psychologist include the allocated costs for IT usage (including hardware and software), hospital space usage, etc. Economic data for these costs was provided from the general ledger for the psychiatric department. However, prior training of staff was not included, but rather the day-to-day costs of administering treatment.
This is now clarified in the manuscript (page 8, first paragraph).

Comment 2:
Cost-effectiveness analysis is not explained in the Analysis section. I am referring to this sentence in the Analysis section: 'In order to avoid biased estimation of uncertainty, we have used the statistical methods of cost-effectiveness to evaluate the joint distributions of costs and benefits.' Cost-effectiveness analysis requires several steps and decisions. Moreover, some readers may not be familiar with this type of analysis. It would add to this paper to explain how this was done and in which way it deviates from traditional cost-effectiveness analysis.

Response:
We have now included the following outline of the steps taken in the cost-effectiveness analysis (see page 9, first paragraph).
"The cost-effectiveness analysis was conducted through the following steps: (1) calculation of costs and effects of each intervention (2) calculation of the differences in cost and differences in effects and (3) calculating the incremental cost and incremental benefit of ICBT versus CBGT and (4) and presenting the distribution of cost/effect differences on a cost-effectiveness plane with confidence interval estimation around the calculated ratio (24). If ICBT is found to be equally effective but less costly, it will be located in the south quadrants of the cost-effectiveness plan close to the y-axis."

Response to Comments from Reviewer 2
Comment 1:

Thanks for providing the uncertainty analysis. The authors may want to state somewhere that even if the original analysis was a "non-inferiority" one, and the results showed that the two approaches can be treated as 'equivalent', but (if I am correct) the direction of effectiveness is still pointing towards the cheaper method, so that the worry on Type II error is not crucial. I would make this discussion explicit and cite the Briggs paper I had mentioned in the previous review.

Response:
We appreciate the comments by reviewer 2 and have now included a discussion on this issue. Specifically, we have included the following paragraph (page 13, third paragraph):
“Fourth, since our study is based on a non-inferiority trial with observed equivalence in treatment effects, the confidence interval suggested some uncertainty around the estimated effect. This concern in cost-effectiveness analyses have been discussed by Briggs and O’Brien (33); in line with the recommendations outlined in the article, we have aimed at providing an appropriate representation of uncertainty using confidence-ellipses on the cost-effectiveness plane.”

Comment 2:
Second, Table 2 shows that changing the discount rate does not change the direction of the cost-effectiveness, which is good. However, it would be interesting to see a similar sensitivity analysis for other assumptions, e.g. the 80% assumption ("the practical capacity of each staff category was estimated to be 80% of the actual number of worked hours"). What happens if one assumes that it is 50% or 100%?

Response:
We appreciate the comments by reviewer 2 and have made further sensitivity analyses, studying the effects of altering the assumption of 80% practical capacity to 50% and to 100%. The results of this sensitivity analysis is presented in the cost-effectiveness acceptability curves, as a method for summarising information on the uncertainty of the assumptions used. We also have included the following paragraph in the methods section (page 8, second paragraph):
“A sensitivity analysis have been performed to study the effects of changing this rate down to 50% or up to 100%, presented in a cost-effectiveness acceptability curve to summarise the uncertainty of the estimates in the cost-effectiveness analysis.”
Further, Fig 2 presents three cost-effectiveness acceptability curves for different assumptions of personnel’s practical work capacity of their full theoretical capacity, illustrating the probabilities that ICBT is cost-effective with changes in the amount that society is willing to pay for a unit increase in health related quality of life, considering healthcare costs. Also, tables 2-4 now includes comparisons across different assumptions of practical capacity.

VERSION 3 – REVIEW

REVIEWER	Wouter van Ballegooijen Vrije Universiteit Amsterdam, Netherlands
REVIEW RETURNED	24-Jul-2017

GENERAL COMMENTS	I thank the authors for addressing my comments.