PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost-effectiveness of therapist-guided Internet-delivered Cognitive Behavior Therapy for pediatric Obsessive-Compulsive Disorder: Results from a Randomized Controlled Trial
AUTHORS	Lenhard, Fabian; Ssegonja, Richard; Andersson, Erik; Feldman, Inna; Rück, Christian; Mataix-Cols, David; Serlachius, Eva

VERSION 1 - REVIEW

REVIEWER	Sandra Hollinghurst University of Bristol. UK
REVIEW RETURNED	01-Dec-2016

GENERAL COMMENTS	This paper describes the economic evaluation of internet-delivered CBT for paediatric OCD. The case for carrying out the study and its context is described well. However, the study has a number of limitations, most of which are listed in the discussion. The sample is very small and the timescale very short, both of which are acknowledged but my main concern is around the data used in the analysis. Resource use data were collected for the 4 weeks prior to the beginning of the study and the 4 weeks at the end of the intervention period. Interpolation was used to estimate resource use for the 12 week period of the study, and then the associated costs for the two patient groups were compared in a before and after way. This seems a bit unconventional and I'm not sure why the authors didn't simply compare the estimated 12-week costs for the two groups, controlling for baseline differences. As it stands, it is difficult to interpret the results - for example, it is hard to understand what the mean cost saving of USD 162 in healthcare utilization (page 20 line 55) in the ICBT group actually means. Perhaps we just need a bit more transparency about the analysis and a justification for the approach. I would like to see a table comparing resource use in the two groups. This is standard practice and a requirement of the CHEERS checklist. I would also have liked more information about the clinician time and platform maintenance costs. It is not clear how the USD 196.86 per participant was estimated and to what extent were these costs fixed or variable. I couldn't see a mention of which year the costs relate to or what exchange rate was used. Parental quality of life woudl have been interesting but I don't think this was considered.

REVIEWER	Clare Rees Curtin University, Perth, Australia
REVIEW RETURNED	25-Jan-2017

GENERAL COMMENTS	This paper makes an important contribution to the literature because it is the first study to report on the cost-effectiveness of Internet-Delivered CBT (ICBT) for paediatric OCD. It is excellent to see that the authors included an analysis of both societal costs as well as healthcare costs. The fact that the EQ-5D-Y was not sensitive enough to pick up improved quality of life associated with reduced OCD symptoms in this study is a very important finding in itself. The suggestion made by the authors to consider using other QALY measures and using more frequent assessment points when assessing cost-effectiveness is useful for the field. One minor requirement is to slightly modify the Conclusion in the Abstract. It states: 'The results suggest that therapist-guided ICBT is a cost-effective treatment and results in societal cost savings, compared to leaving patients untreated'. As the wait-list control group were possibly accessing psychosocial supports/other treatment (but not CBT) its not exactly true to say that they were 'untreated'. I think it would be more accurate to say that they were not receiving evidence-based treatment. Minor Corrections: Page 7, Line 37, Remove the word 'of' from: 'increased of academic'. Page 16, Line 14, 'Resulting into a...' should be 'resulting in'.

REVIEWER	Lidewij Wolters Norwegian University of Science and Technology (NTNU), Faculty of Medicine; Regional Centre for Child and Youth Mental Health and Child Welfare (RKBU Central Norway), Norway
REVIEW RETURNED	26-Jan-2017

GENERAL COMMENTS	The present paper presents an investigation of the cost-effectiveness of an internet-delivered CBT (ICBT) treatment program for adolescents (12-17 yrs) with OCD. Costs and health related outcomes for the intervention were compared to a waitlist control condition. Data were collected pre- and post-treatment. Sixty-seven adolescents with OCD participated (33 ICBT; 34 waitlist control). Results indicated a significant reduction in costs for ICBT compared to the control condition (no treatment). The study adds to the existing literature as there are hardly any studies on cost-effectiveness of internet-delivered treatment programs (especially for youth), despite a rapid rise in the development of such treatments. The results may have implications for clinical practice and policy, specifically for those patients who otherwise would have no access to treatment. The manuscript is well-written, the analyses seem adequate and are clearly described. I have a few minor comments. The authors do not describe how the patients were recruited (e.g., patients referred for treatment, advertisements in newspapers,

	internet, …). Could the authors add this information and possible implications (e.g., select sample)? The patients' characteristics as shown in table 1 give the impression of a relatively highly-educated, native sample. This may restrict the generalization of results to other samples. It would be interesting to read the authors' opinion on this topic (added to the discussion section). Table 2: It was not clear to me how to interpret the symbol '*' ('negative values indicate cost savings of ICBT compared to waitlist') in the columns 'mean change pre- to post-treatment' for the ICBT and the waitlist condition. I would expect that the mean change pre- to post-treatment for a single condition (ICBT or waitlist) does not contain a comparison between treatments. Could the authors please explain what is meant? Unfortunately, due to an error it was not possible to include loss of parental productivity in the analyses. Addition of such data may affect the results (loss of parental productivity may lead to substantial costs), and therefore I suggest to mention this limitation in the discussion section. Could the authors please check reference 32 (Hess et al., 2016). I hope these comments will help to strengthen the paper.

REVIEWER	Joseph F. McGuire University of California Los Angeles United States of America
REVIEW RETURNED	28-Jan-2017

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript and offer my comments on it. This paper presents a cost effectiveness analysis of a therapist guided-internet delivered cognitive behavior therapy (ICBT) for childhood obsessive-compulsive disorder (OCD) delivered in the context of a randomized controlled trial. Participants were 67 adolescents recruited in Sweden and were randomly assigned to a 12-week ICBT intervention or a 12-week waitlist control condition. The authors conducted a comprehensive cost and cost effectiveness analysis that examined costs in terms of both total societal costs (intervention costs and other societal costs) and total health care costs (intervention costs, costs for healthcare utilization). The authors found favorable cost analyses of ICBT relative to the waitlist condition of approximately 144 USD, and only an added average healthcare cost of 21USD per patient. Although OCD symptom severity significantly improved in the ICBT condition relative to the waitlist, there was no significant benefit for secondary health outcomes such as quality adjusted of life years (QALYs). Cost effective analyses revealed an overall probable cost savings in favor of ICBT with a favor incremental cost effectiveness ratio (2.29 USD per responder) that was 100% at 200 USD per responder. The authors appropriately conclude that ICBT, relative to the waitlist condition, provides cost savings and is cost effective. This manuscript had several strengths such as the innovation of the

	intervention, strong writing, and rigorous methodology. Moreover, it addresses an important topic, providing evidence-based care to youth with psychiatric conditions in a cost efficient/effective manner. The following comments are provided to further strengthen a meaningful contribution to the literature. Abstract: 1. The abstract was well-written. Introduction: 1. The introduction is well written and provides a good rationale for the current paper. However, a minor point. Given the emergence of face-to-face video teleconferencing technology that some have used to deliver CBT, it would be helpful if the authors added a line to distinguish the difference between the I-CBT provided in this study and video teleconferencing CBT. Methods & Results: 1. The methods and results sections are appropriate and well-written. Although I was a bit surprised that there was no significant improvement in quality of life for the ICBT group, the intervention appeared to specifically target OCD symptom severity. Thus, these effects may not have readily generalized to quality of life. The authors may note (in the discussion) that the inclusion of therapeutic modules in the ICBT intervention focused on quality of life may more directly improve this outcome. Discussion: 1. Given that this study focused on ICBT versus a waitlist control condition in which only 18% of participants were on an SSRI medication, these study findings are a bit circumscribed to the cost and cost effectiveness of ICBT relative to minimal intervention. I am curious if these cost analyses would be similar in other developed countries? Perhaps could this be a model for treating childhood psychiatric conditions in developing countries where expert mental health care providers are sparse? A little more information on this in the discussion would be welcome. 2. Additionally, it would be informative if the authors reported how these cost and cost-effective analyses compare to other studies in OCD whether for ICBT (e.g., Andersson et al. 2015) or other treatment modalities for OCD. This would help frame the authors' findings relative to current approaches and/or prior ICBT studies. 3. On page 21, the authors state that "the finding that therapist-guided CBT is a cost-effective treatment...suggests that integrating ICBT within the regular armamentarium of specialist OCD clinics or even regular child and adolescent psychiatry units is likely to be a worthwhile investment for society." While I agree with the sentiment that ICBT presents considerable therapeutic benefit, it might be better to soften the language due to the emerging state of the literature and need for further research. For instance, it might be better to reframe ICBT as demonstrating "considerable promise" and "addressing several treatment gaps." The authors could also consider noting that further research is needed to compare ICBT with a stepped-care approach for a more active comparison intervention.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Sandra Hollinghurst

1. Resource use data were collected for the 4 weeks prior to the beginning of the study and the 4 weeks at the end of the intervention period. Interpolation was used to estimate resource use for the 12 week period of the study, and then the associated costs for the two patient groups were compared in a before and after way. This seems a bit unconventional and I'm not sure why the authors didn't simply compare the estimated 12-week costs for the two groups, controlling for baseline differences. As it stands, it is difficult to interpret the results - for example, it is hard to understand what the mean cost saving of USD 162 in healthcare utilization (page 20 line 55) in the ICBT group actually means. Perhaps we just need a bit more transparency about the analysis and a justification for the approach.
Response: Thank you for bringing this important issue to our attention. We agree that the estimation of costs should be clarified. Our approach aims to estimate the full costs of all 12 weeks of ICBT or waitlist. A limitation, however, of the chosen resource use measure (the TIC-P) was that it captures merely the last four weeks. As the study period was 12 weeks, using only the week 0 and week 12 measurement points, would consequently neglect the costs of week 4 and week 8. We therefore calculated the costs of weeks 4 and 8 using linear interpolation (following the notion that OCD symptoms change linearly over time, and that costs would follow the same trajectory). To give an example, if week 0 costs were 1000USD and week 12 costs were 2500USD, week 4 costs would have been estimated to 1500 and week 8 costs to 2000USD. The change score in this case would have been the sum of week 4, 8 and 12 costs with week 0 set to zero (500 + 500 + 500 = 1500), and by that controlling for baseline differences. In a last step, we compared the differences between the change scores of ICBT and the waitlist control, with positive values indicating additional costs of ICBT over the 12 weeks, compared to waitlist, and negative values indicating additional cost savings of ICBT compared to waitlist.
We have clarified our approach accordingly in the methods section and hope that this is now more transparent and intuitive for the reader.

2. I would like to see a table comparing resource use in the two groups. This is standard practice and a requirement of the CHEERS checklist.
Response: Thank you for this suggestion, such a table is now added as an online supplement (supplement 2).

3. I would also have liked more information about the clinician time and platform maintenance costs. It is not clear how the USD 196.86 per participant was estimated and to what extent were these costs fixed or variable.
Response: The clinician times were logged by the platform and we had therefore individual patient clinician times, which then were multiplied with the average clinician salary, thus an individual cost for every patient. Regarding the platform maintenance costs, we used the actual annual cost for support and technical updates and calculated it for a 12 week period, divided by number of patients, thus estimating a fixed cost per patient for 12 weeks of ICBT. This is now clarified in the manuscript, see page 11.

4. I couldn't see a mention of which year the costs relate to or what exchange rate was used.
Response: We used the purchasing power parity values to change SEK 2014 to USD 2016 using the International monetary estimates. Please find this more clearly stated in the manuscript now, page 11.

5. Parental quality of life would have been interesting but I don't think this was considered.
Response: We agree, and especially as there is strong evidence from the paediatric OCD field that

parental psychosocial and occupational functioning is affected by the child's or adolescent's symptoms, we believe both a cost evaluation as well as an evaluation of the parents' quality of life would have been very interesting. We did not have the according data in the current trial, but agree that this would be a valuable addition in future studies.

Reviewer: 2
Reviewer Name: Clare Rees

1. One minor requirement is to slightly modify the Conclusion in the Abstract. It states: 'The results suggest that therapist-guided ICBT is a cost-effective treatment and results in societal cost savings, compared to leaving patients untreated'. As the wait-list control group were possibly accessing psychosocial supports/other treatment (but not CBT) its not exactly true to say that they were 'untreated'. I think it would be more accurate to say that they were not receiving evidence-based treatment.
Response: Thank you for bringing that to our attention, this is now changed accordingly, see the abstract.

2. Minor Corrections: Page 7, Line 37, Remove the word 'of' from: 'increased of 3. academic'. Page 16, Line 14, 'Resulting into a...' should be 'resulting in'.
Reponse: This is now corrected.

Reviewer: 3
Reviewer Name: Lidewij Wolters

1. The authors do not describe how the patients were recruited (e.g., patients referred for treatment, advertisements in newspapers, internet, …). Could the authors add this information and possible implications (e.g., select sample)?
Response: Thank you for pointing this out. We provide now more information about the recruitment of patients (page 8).

2. The patients' characteristics as shown in table 1 give the impression of a relatively highly-educated, native sample. This may restrict the generalization of results to other samples. It would be interesting to read the authors' opinion on this topic (added to the discussion section).
Response: We agree that the high proportion of self-referrals as well as high levels of parental education could indicate a selected sample, with important limitations for generalizability to patient populations typically found in mental health care contexts. We discuss the implications of this now in the discussion section, page 23.

3. Table 2: It was not clear to me how to interpret the symbol '*' ('negative values indicate cost savings of ICBT compared to waitlist') in the columns 'mean change pre- to post-treatment' for the ICBT and the waitlist condition. I would expect that the mean change pre- to post-treatment for a single condition (ICBT or waitlist) does not contain a comparison between treatments. Could the authors please explain what is meant?
Response: Indeed, the comment referring to the * makes no sense in the columns that report the change scores for ICBT and waitlist group, and the stars are now edited out from the table, with exception from the ICBT vs waitlist difference column. Thank you for noticing this error.

4. Unfortunately, due to an error it was not possible to include loss of parental productivity in the analyses. Addition of such data may affect the results (loss of parental productivity may lead to substantial costs), and therefore I suggest to mention this limitation in the discussion section.
Response: We agree that it would have been interesting to include parental productivity loss in the analyses, especially as the literature on family function within paediatric OCD indicates that parents of

kids with OCD suffer significant impairments in social and occupational functioning. This is now mentioned in the limitations, page 23.

5. Could the authors please check reference 32 (Hess et al., 2016).
Response: The correct reference is Mataix-Cols et al., 2016, and is now changed accordingly.

Reviewer: 4
Reviewer Name: Joseph F. McGuire

Introduction:
1. The introduction is well written and provides a good rationale for the current paper. However, a minor point. Given the emergence of face-to-face video teleconferencing technology that some have used to deliver CBT, it would be helpful if the authors added a line to distinguish the difference between the I-CBT provided in this study and video teleconferencing CBT.
Response: Thank you for this suggestion, which is certainly helpful for the readers to differentiate between the ICBT presented in our study, and teleconferencing or telephone-based CBT. Such a statement is now included, see page 5f.

Methods & Results:
1. The methods and results sections are appropriate and well-written. Although I was a bit surprised that there was no significant improvement in quality of life for the ICBT group, the intervention appeared to specifically target OCD symptom severity. Thus, these effects may not have readily generalized to quality of life. The authors may note (in the discussion) that the inclusion of therapeutic modules in the ICBT intervention focused on quality of life may more directly improve this outcome.
Response: We were indeed surprised to find no change in the quality of life measure, EQ5D-Y, while finding significant symptom reductions in the OCD symptoms in the ICBT group. After a thorough clinical evaluation of the measure, we concluded that the EQ5D-Y is not measuring quality of life aspects that would be considered as relevant in adolescents with OCD, as only one item asks about psychological well-being, and the remaining four items are concerned with rather somatic functioning (such as mobility issues and pain). In addition, the EQ5D-Y correlated non-significantly with the CY-BOCS, thus further strengthening our impression of its questionable validity for paediatric OCD patient populations.
Because of these rather psychometric concerns, we would argue that the intervention most likely produced symptoms reductions as well as an increase in everyday function and quality of life, but that the chosen questionnaire was not able to measure these variables accordingly, which is discussed on page 21f.

Discussion:
1. Given that this study focused on ICBT versus a waitlist control condition in which only 18% of participants were on an SSRI medication, these study findings are a bit circumscribed to the cost and cost effectiveness of ICBT relative to minimal intervention. I am curious if these cost analyses would be similar in other developed countries? Perhaps could this be a model for treating childhood psychiatric conditions in developing countries where expert mental health care providers are sparse? A little more information on this in the discussion would be welcome.
Response: This is an interesting suggestion, and it puts this line of research in a more global health care perspective, which we find is very relevant. We have added a discussion point of this in the discussion section, page 21.

2. Additionally, it would be informative if the authors reported how these cost and cost-effective analyses compare to other studies in OCD whether for ICBT (e.g., Andersson et al. 2015) or other treatment modalities for OCD. This would help frame the authors' findings relative to current approaches and/or prior ICBT studies.

Response: Thank you for this suggestion. Optimally, our results warrant comparisons from within the ICBT field or other interventions of paediatric OCD, preferably standard face-to-face CBT or pharmacotherapy. The Andersson et al., 2015 study was a cost-effectiveness analysis of additional booster sessions of ICBT, and we find it therefore not an appropriate comparison to our study. Surprisingly, to the best of our knowledge, there is no available cost data from the paediatric OCD field, neither on CBT or pharmacotherapy, and therefore we do not have the possibility to evaluate our results in the light of other relevant cost-effectiveness data. As we point out in the introduction, ICBT in adult populations is considered a cost-effective intervention. However, we agree that more cost-evaluations are needed in the paediatric OCD field as well as the field of ICBT for children and adolescents.

3. On page 21, the authors state that "the finding that therapist-guided CBT is a cost-effective treatment...suggests that integrating ICBT within the regular armamentarium of specialist OCD clinics or even regular child and adolescent psychiatry units is likely to be a worthwhile investment for society." While I agree with the sentiment that ICBT presents considerable therapeutic benefit, it might be better to soften the language due to the emerging state of the literature and need for further research. For instance, it might be better to reframe ICBT as demonstrating "considerable promise" and "addressing several treatment gaps." The authors could also consider noting that further research is needed to compare ICBT with a stepped-care approach for a more active comparison intervention.
Response: We have revised the according formulation and also integrated, as suggested, the notion of a stepped-care approach, which we find very convincing and intuitive.

Additional changes in the revised manuscript:
Please note that we found an error in the presented cost per responder estimate, which now is corrected in the abstract and results section (the cost of an additional responder in ICBT is 78 USD). Accordingly, the cost-effectiveness acceptability curve (Figure 3) has been updated.

VERSION 2 – REVIEW

REVIEWER	Lidewij Wolters NTNU (Norway); AMC (the Netherlands)
REVIEW RETURNED	07-Mar-2017

GENERAL COMMENTS	The authors have sufficiently addressed the reviewer's comments.

REVIEWER	Joseph F. McGuire Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles
REVIEW RETURNED	07-Mar-2017

GENERAL COMMENTS	The authors have done an excellent job of addressing the comments that I raised in my previous review. I have no further recommendations to offer at this time, and look forward to the publication of this important contribution to the literature.

Corrections: Cost-effectiveness of therapist-guided internet-delivered cognitive behaviour therapy for paediatric obsessive-compulsive disorder: results from a randomised controlled trial

Lenhard F, Ssegonja R, Andersson E, *et al*. Cost-effectiveness of therapist-guided internet-delivered cognitive behaviour therapy for paediatric obsessive–compulsive disorder: results from a randomised controlled trial. *BMJ Open* 2017;7:e015246. doi: 10.1136/bmjopen-2016-015246

This article has been corrected since it first published. The legends of Figures 2 and 3 have been swapped round as these were typeset in the wrong position.

BMJ Open 2017;**7**:e015246corr1. doi:10.1136/bmjopen-2016-015246corr1