Author's response to reviews

Title: Acceptability, effectiveness, and cost-effectiveness of internet-based exposure treatment for irritable bowel syndrome in a clinical sample: a randomized controlled trial

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Version: 4 Date: 8 August 2011

Author's response to reviews: see over
We were happy to note that the reviewers judged we had followed their recommendations. In this second revision we have reworked much of the background and discussion with the aim of making them more succinct.

**Reviewer:** Yanda van Rood

**MCR**

*Firstly, the authors are advised to let their manuscript be corrected for English style and specifically pay attention to the phrasing of sentences and use of commas. The authors use the personal style (‘we’ / ‘our’) often (39 / 29 times) also in parts of the manuscript were a impersonal (academic) style is expected (methods, analysis and results). Furthermore, the background and discussion are very long and they both need structuring; i.e. a paragraph per subject and subjects logically following from each other. This would improve reading and lead to a reduction of the number of words since at a number of occasions the authors repeat themselves.*

We have done thorough copyediting of the manuscript and followed the reviewer’s guidelines. We hope that this has resulted in a more acceptable English style and a more logical flow.

**MER:** *The title includes feasibility and cost-effectiveness but effectiveness is missing from it.*

We have added effectiveness to the title.

**MCR:** *In the method section the authors describe how they study effectiveness and cost-effectiveness but feasibility is not defined. Instead of feasibility the authors might want to focus on acceptability instead since acceptability and compliance seem more relevant aspects of the study than feasibility. Acceptability and compliance to the treatment regime were low as is suggested by the high dropout rates (also before randomization) and the fact that only 43% of the patients worked through all the steps of the program.*

We have now removed “feasibility” from the manuscript and added “acceptability” instead. The relatively low acceptability is highlighted in the abstract and the discussion of the manuscript.

**MER:** *In the method section, e.g. treatment condition, background information is given that might be better placed in the background section.*

We agree with the reviewer that the first paragraph under the Treatment condition heading would traditionally be placed in the background. However, we believe that this would somewhat make the Background less distinctively focused on previous ICBT/minimal contact CBT-trials and their recruitment methods – which is the primary background for this trial. We believe that keeping the first paragraph in the Treatment section there will make the background more straightforward and it also ties together with the treatment rationale and contents. However, if the Editor agrees we are of course prepared to move the first paragraph under the Treatment condition heading to the
background.

**MER:** In the analysis section the authors describe that they used all available data on the assumption of MAR, i.e. missing at random. However, one might question the randomness of the missing data especially since the data itself give the impression that the missing of data might be associated with lower acceptability and/or compliance to treatment of patients with more severe IBS complaints. The authors might want to describe how this assumption was tested or made plausible.

Under the assumption of MAR, there may be observed variables that are related to data missingness, such as more severe IBS symptoms, and as long as they are included in the model it is considered to give unbiased estimates. This is explained in the analysis section (“FIML under the assumption of MAR requires that observed variables that are associated with the likelihood of data missingness are included in the analysis [54]. Prior to conducting the primary analysis, the missing data mechanism was assessed by exploring the relationships between baseline characteristics and the presence of missing data in the sample.”). It is not possible to test if the assumptions of MAR are met (cf. Salim et al. Psychiatry Research (2008) vol. 160), since they are violated when data missingness is dependent on unmeasured variables (e.g. post-treatment values).

**DR:** Results. The intervention is aimed at breaking the vicious circle by reducing anxiety and avoidance behaviour. Pearson correlations between the change scores of IBS symptoms and anxiety and avoidance measures, would give some insight in the relation between these two aspects and mechanisms that play a role in the reduction of IBS symptoms (mediators).

We have considered the reviewer’s suggestion but decided not to include a mediational analysis in the manuscript. This is for two reasons. First, to report a correlation between change scores would not be very informative. Since both scores decrease in the ICBT group this is to be expected (and is indeed the case as our calculations show). But this is not sufficient to establish mediation since the mediator and outcome are measured at the same time. Proper mediational analyses require more complex statistical models and we plan to publish properly analyzed data from our AJG study. Second, the manuscript has grown a lot with the addition of cost-effectiveness and prediction analyses and as the reviewer previously pointed out the discussion is quite long. We fear that adding even more analyses may make the article too long and even less to the point.

**MER:** Page 9 first sentences Figure 1 needs to be Table 1. Please check, on 11 occasions Figure is used, were in some instances Table is meant.

We have searched through the manuscript and could not find a single instance of referring to a Figure when a Table was meant (or vice versa). However, we had not renumbered the Table references since Table 2 was added, this has been fixed.

**DR:** In the discussion the authors should present firstly the results concerning feasibility (or better acceptability), effectiveness and cost-effectiveness before discussing them.
Furthermore, in the discussion the authors might want to refer to other studies as well as to their own previous study. Specifically studies showing that certain interventions are most suited for patients with less severe symptoms.

We now mention the results regarding acceptability and cost-effectiveness early in the discussion. Regarding other studies indicating that patients with worse symptoms are less likely to benefit from treatment we do not believe that any such data are available, at least not for IBS patients (as we mention in the discussion, attempts to predict treatment response have not been successful in IBS). In fact, our previous studies, that included more impaired patients, had more favorable treatment outcome. We now highlight this in the discussion and conclude that more research is needed before we can determine for which patients ICBT is acceptable and suitable.

DR: The results suggest that this specific ICBT intervention is best suited for patients with less severe IBS complaints, anxiety and avoidance behaviour. In the discussion the authors might want to bring forward that the intervention could be offered as a first step in a stepped care approach and could best be offered to patients in primary practice who have generally less severe complaints than patients visiting an outpatient GE clinic. These patients are probably also more like the self referred and specialist referred patients from the earlier study.

As we mention in our previous comment this does not seem to be the case, that our “treatment successes” have been primary care patients with less severe symptoms.

DR: The effect-size observed in the earlier study was large, the effect-size in the current study was moderate. “Somewhat larger” does not accurately describes the difference.

Changed accordingly!

Reviewer: Rona Moss-Morris

1. ... ‘at the end of treatment’ or ‘at 10 weeks’ should be added to the following hypothesis.

Hypothesis 1:
Our primary hypothesis was that, compared to a waiting list, ICBT would lead to greater reductions in IBS-symptoms.

Changed accordingly.

2. The authors have misinterpreted my point about ITT. I wasn’t suggesting using last observation forward as I agree; modeling has now replaced this method. However, if you have data for at least one follow-up, a mixed model will keep these people in the model. Therefore a better way to assess if gains were maintained at 12 months without losing such a large percentage of cases is to include all 3 time points for the treatment group in the model. I realise this would be difficult for the post treatment comparison between groups as there is only one follow-up point, so perhaps in this context, what the authors have done with the last observation forward is one way to test what happens if all people...
We agree that it would have been preferable to include all time-points in the model (as we did in our AJG article), but as we don't have any “untreated” data for the waiting list at follow-up that model would not make any sense. But we have now added sensitivity analysis to the maintenance-of-improvement test that is done with the follow-up data as the reviewer previously suggested.

We thank the reviewers for reading our manuscript and giving valuable comments. We also thank the editor for inviting us to resubmit our revised manuscript.