Author's response to reviews

Title: The (cost) effectiveness of an online intervention for pregnant women with affective symptoms: protocol of a randomised controlled trial

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Author's response to reviews: see over
Dear Mrs Cruz,

At first we will thank you, the BMC and especially the referees for making effort to review our article. We have answered the questions of the referees to the best of our knowledge and adjusted the manuscript according to their propositions. We organised our response as followed: first repeating the successive questions in the cover letter, followed by formulation of our responses and lastly highlight the changes in the revised manuscript.

We will start with the first referee, Mrs. Lopez and thank her for her friendly words addressing our study.

To begin with your first question.

1. *This study propose an interesting intervention to decrease affective symptoms and their consequences in pregnancy, birth and postpartum. The study is original, innovator and pertinent. The trial is well explained and justified by evidence. The most of references are about depressive symptoms or depressive disorder; even those refer affective symptoms, please review.*

Reviewing the literature reveals a lot of articles about the anxiety symptoms in pregnancy, but the difficulty is that in most articles the differentiation between anxiety and depressive symptoms and/or anxiety and (acute) stress is not properly made. There are however sparse studies which do make a distinction between anxiety and depressive symptoms and for example their influence on the development of a postpartum depressive disorders. We include these studies in our references. The adjusted references will include:


2. *About method, I probably use the term “control group” more than “waiting list group”, because is not exact.*
We deliberately choose the term ‘waiting list group’ to give a more accurate definition of our control group. It expresses that this group has no condition other than the possibility to participate in the intervention at the end of follow-up, 6 weeks after giving birth. Naturally the participants of the control group are free to seek other treatment of help to alleviate their depressive and anxiety symptoms. In case of very high scores on the CES-D and/or the HADS-A we will strongly advice them to do so. Therefore we would like to maintain our terminology of “waiting list group”

I would like to remark the need for following of women who are rejected by suicide attempt or those who are severe depression. I consider that researches must be to be sure that they are attended for her GP or specialist. This is especially relevant in people with suicide thinks or women who are in severe depression or anxiety and they are in control group.

We have a lot of experience in online interventions for people with depressive disorders and even with suicidality.


However in this study we decided to exclude women with suicidal plans. They will be referred to their general practitioner... In the Netherlands the general practitioner has in important function in coordinating all the health issues of the patients. He or she knows the ways in the region to deliver adequate additional mental service. We will discuss the referral during a phone-call. If then there are any doubts about the safety of the patients, we will also contact the GP ourselves. For that reason we ask all participants the name of their general practitioner.

Women with severe depressive symptoms are not rejected. We will include them since we know that those very people will probably also benefit from the intervention (Bower P., Kontopantelis E., Sutton A., Kendrick T., Richards D.A., Gilbody S., Knowles S., Cuijpers P., Andersson G., Christensen H., Meyer B., Huibers M., Smit F., van Straten A., Warmerdam L., Barkham M., Bilich L., Lovell K. and Tung-Hsueh Liu E.: Influence of initial severity of depression on effectiveness of low intensity interventions: meta-analysis of individual patient data. BMJ 2013, 346:f540 doi).

However they will get the advice to contact their GP to receive additional care

Not for this trial, but the next study I suggest doing the recruitment in obstetrician
or primary care and to collect data about reject or impossibility to have access to the study. As well is said by the authors one of the limitations is the access of this intervention of general population, especially some groups of women in risk to suffer affective disorder in pregnancy and postpartum. The results are not easily applicable for general population.

We prefer to perform the study among the general population because in this way we might reach more people than through health care (obstetrician or primary care). About 95% of the Dutch people have access to the Internet and many people with health problems first consult the Internet before seeking help from a care provider. Also after the study the intervention might be offered to the general population. You are right that people recruited in this way might be different than the ones presenting themselves in health care. We agree that in a next study it would be interesting to examine those differences.

3. Maybe the authors can reference studies that show that this kind of online intervention is recommendable for severe depression or anxiety symptoms.


Both references are incorporated in the article

4. About moment of evaluation, it is said that there is an evaluation post treatment, but it is not clear why this evaluation is 10 week after inclusion, if treatment takes only 6 weeks.

We apologize that we didn’t describe the reason for evaluating the intervention after 10 weeks instead of 6 weeks. Although it is possible to complete the intervention in 6 weeks there are
always a number of participants who need more time. To be sure to assess everyone after completing the intervention we expanded the follow-up time to 10 weeks. We adjusted the text by adding the next sentence in the assessment section: ‘(although it is possible to finish the intervention in 6 weeks we know that there will be some people who need more time. To ensure that the post-test assessment takes place after completing the intervention we will perform the post-test assessments after 10 weeks.’

Is not specified how to consider compliance of treatment: if women finish all sessions in time (one by week); if they finish the sessions in 10 weeks; if it’s consider withdrawal when they don’t do it the homework; etc.....

Even, is not explicit if therapist take contact with them if she doesn’t entry the programme, follows the session, does homework, etc...

We consider a participant as compliant if she finishes all lessons in 10 weeks. After 10 weeks it is still possible to complete the intervention, however without support. If it takes the participant more than one week to finish a lesson she will receive a reminder by mail. If she does not react she receives another 2 mails before considering her as drop out.

5. I’m afraid about the drop out, not only of women who are in control group, even those who are doing the programme. Evaluations take time, and the PTS requires concentration and attention, and it could be very tired for pregnant women.

We know from other online treatments in depressed patients that drop-out is usually not much higher than for face-to-face treatments. In this population it might be higher or lower. The uptake of the intervention, and therefore the acceptability to patients, is one of our study outcomes.

6. Probably it would be enough if the experience psychiatrist reviews some feedback by random, not all the feedbacks

We thank you for the suggestion. Our plan is to review everything at the start of the interventions and when the therapists are more experienced only do so randomly.

7. Measures: Maybe it would be interesting to introduce some measure about complications previous of birth (e.g. haemorrhage, diabetes...).
This is a very good idea. We ask for this kind of complications by means of the TIC-P questionnaire. In this questionnaire we ask for complications in previous pregnancies or during childbirth.

8. About references:

Please, review references from 27 till 35 (36 and 37 are not cited).

Better use "-", that numbered references e.g. (4,8-10); (32-34)

Thank you for the suggestion. We have reviewed the references as suggested and adapted the text.

The next answers are directed to the questions of Mrs Austin. We also thank her for her review.

1. Introduction: needs to clearly describe the protocol on which this current protocol seems to be based as per publications 22 and 23, at present this only comes out in the methods section.

To make it clear on which protocol our intervention is based we made a small change to the introduction. We also refer to the methods section for further explanation. We adjusted the introduction as follows: ‘We will examine the effectiveness of an intervention based on an existing, evidence based internet self help version of PST (19) compared to a waiting list control condition on (1) the reduction of depressive and anxiety symptoms post intervention, end of pregnancy and 6 weeks postpartum and, (2) the improvement in perinatal outcomes (for example pre-term birth, growth restriction and breastfeeding initiation). We will also (3) determine cost-effectiveness using a societal perspective (see also method section).’

2. Sample choice: is problematic in that it is very heterogeneous and includes mild to severe symptoms with allowance for women on medication or having psychotherapy which are very major confounders.

This trial is a pragmatic trial which studies effectiveness (instead of efficacy). Therefore, we aim to include the same patients who might present themselves for this intervention after the trial has ended. We are specifically interested in the effects among this (heterogeneous) population. Furthermore, we expect that the percentage of women in the intervention group using medication (or receiving psychotherapy) will equal the percentage of women in the control group receiving medication or psychotherapy (our randomization will ensure that).
Therefore, the differences in outcomes between the two groups can still be attributed to the online intervention. This design is similar to one of earlier studies (among the general population) on the same intervention (Van Straten A, Cuijpers P, Smits N: Effectiveness of a Web-Based Self-Help Intervention for Symptoms of Depression, Anxiety and Stress: Randomized Controlled Trial. J.Med.Internet Res 2008, 10:e7).

3. Stats: this section does not explain how these key confounders will be controlled for.

We do not expect confounders to be an important problem. As explained before, we expect that confounders are equally distributed between arms. However, will of course (1) check if we succeed in our randomization and the equal distribution of confounders and (2) take possible confounders into account when calculating the significance of the effects between groups (ANOVA’s).

Minor revision:

uptake of healthcare services (TiC-P) is referenced as number 31; this is incorrect as that is a reference to EPDS.

We have made revisions of all references

We finally want to thank the third referee Thinh Nguyen for the comments made on our article. Our manuscripts have been improved because of this.

1. The strength of this study is in having two sets of outcomes, one clinical and the other economic, i.e. cost saving. However the economic analysis is quite vague and requires elaboration. There are references made to "indirect costs", "bootstrap replications", and "cost utility analysis" and incremental cost-effectiveness ratio (ICER), without explanations of what they mean, or exactly how the analyses are done. This is particularly important in addressing ways in which savings can be made for the intervention group compared to control control. It may be helpful to cite previous work using the same sorts of analyses.

We thank you for pointing out that our chapter on economic analysis is not clear enough to our readers. We have adjusted the paragraph ‘economic analysis’ according to your directions. The changes are as follows:

**Economic analysis**
The economic analyses are undertaken from a societal perspective, taking into account intervention costs, direct medical costs, direct non-medical costs and indirect costs during the study period [38]. Indirect costs refer to lost resources and opportunities resulting from the disease.

We will assess health service uptake and production losses at T0, T1, T2 and T3 based on the TIC-P. Full economic costs due to care utilisation and production losses are obtained from the national manual for cost prices in the health care sector. The intervention costs concern the costs related to the internet application, the advertisement and the training/salary of the coaches. Indirect costs include production losses both in paid labour and in the domestic sphere. In addition, both costs due to work loss and work cut-back are assessed, as work cut-back in patients with affective symptoms may be substantial. To calculate indirect costs the friction cost method is used, thereby taking the replacement of sick employees into account, resulting in more conservative cost estimates than the human capital approach. As the timeframe used in the present study is relatively short, costs are not discounted nor corrected for inflation.

To account for the possible non-normality of the cost data, sample errors and 95% confidence intervals are based on resampling methods (bootstrapping) using 2,500 replications.

A cost-effectiveness analysis assesses the costs per recovered patient [39]. Quality of life is assessed at each assessment point with the Euroqol, and the average quality of life during the study period is calculated.

A cost-utility analysis is similar to a cost effective study, but assesses the incremental costs per QALY gained during the study period (instead of the incremental costs per recovery). We will report the incremental cost-effectiveness ratio. The Incremental cost-effectiveness ratio (ICER) is the ratio between the difference in costs (between experimental and control condition) and the difference in effects (between experimental and control condition), where costs is the average annual per capita cost and effects is the percentage of participants that recovered from their depression.

The ICER, the scatter of the bootstrapped ICERs on the ICER plane and the ICER acceptability curve for the probability that the intervention dominates care as usual for a series of willingness-to-pay ceilings. Use will be made of the pertinent guidelines for health economic evaluation.

We also added a reference referring to previous work using the same sorts of analysis.
2. The manuscript will benefit from a study flow chart, to illustrate the process of selection and randomisation as well as timeline (T0, T1, T2 and T3).

We included a study flow chart. See below and in the article in the assessment section

Flowchart selection, inclusion, intervention and measurement

Registration via website,

Signed informed consent received

Link to first questionnaire (T0) and user information is sent by mail

T0 is completed.
  If CES-D>16 en /of score >8 op de HADS A respondent can be included.
  If the WSQ = 3 the respondent is called and on the base of this conversation a decision about the inclusion is made. The general practitioner will be informed.
  If the scores are high (CESD ≥ 25 or HADS-A ≥ 12) the participant will be advised to look for additional care in consultation with her GP

Randomisation in intervention and waiting list group

If the respondent has a low score an exclusion mail is sent.

10 weeks after T0 respondents receive T1

4 weeks before expected childbirth respondents receive T2

6 weeks after childbirth respondents receive T3
3. The authors need to address confidentiality and how personal information collected will be safeguarded.

All personal information is stored on a computer network which is only accessible for the main researchers and data managers. They all have to sign an affirmation of confidence. Analyses will be performed on anonymised data only. In accordance with Dutch law, the research protocol has been reviewed by our Medical Ethical Committee and been approved.

4. The reference is made to "trained coaches", what does this mean? How are the therapists trained? Reliability?

The coaches are psychologists, psychiatrists and master students in psychology. They receive a three hour training and are closely supervised by an experienced psychologist, which means that all feedback to the participants is read and commented by her. We made the following adjustment in the article (intervention section)

Minor essential revisions

1. The term "dysmaturity" was used on several occasions, without definition of what it means. Similarly what is meant by "affective dysregulation"? Do the authors mean affective disorders such as depression?

The meaning of dysmaturity is small for gestational age and is commonly defined by a foetal weight below the 10th percentile as determined by ultrasound... We will adjust this in the text in the abstract section:

‘Affective disorders in pregnancy are associated with an increased risk of prematurity, dysmaturity (foetal weight below the 10th percentile as determined by ultrasound) and the development of postpartum depressive disorder.’

The meaning of affective dysregulation is a mood dysregulation consisting of depressive and/or anxiety symptoms. We will adapt the text in the background section in order to clarify:

‘Women in pregnancy and postpartum have an increased vulnerability to develop a depression or anxiety disorder, both affective disorders. The prevalence of depressive and anxiety disorders during pregnancy is 12 and 11% respectively [1]. The prevalence rate of mild affective symptoms is estimated to be 17% [2]. Affective dysregulation (mood dysregulation consisting of depressive and/or anxiety symptoms) in pregnancy is often not diagnosed because of overlapping symptomatology with pregnancy itself. It remains therefore often not recognised [3].’
2. The authors may want to discuss barriers to seeking treatment in perinatal psychopathology (i.e. too busy to attend appointments) and how internet intervention (can be done at anytime) may improve treatment uptake.

Barriers as suggested by the reviewer have been briefly mentioned in the introduction:
“Internet interventions are easy accessible, home-based and can be followed in one’s own time. There is no waiting list and there is also a reduction in therapist time and costs.”

I hope I have answered all questions sufficiently and satisfactory and am looking forward to hear from you.

On behalf of all the authors,
Hanna M.Heller Md