Author's response to reviews

Title: An Economic Evaluation of an Augmented Cognitive Behavioural Intervention vs. Computerized Cognitive Training for Post-stroke Depressive Symptoms

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Author's response to reviews: see over
To: Editor, BMC Neurology

Maastricht, November 6th

Dear editor,

Please find enclosed our revised manuscript entitled ‘An Economic Evaluation of an Augmented Cognitive Behavioural Intervention vs. Computerized Cognitive Training for Post-stroke Depressive Symptoms’ (MS: 4010554501734941) by Mitchel van Eeden, Joyce Kootker, Silvia Evers, Caroline van Heugten, Alexander Geurts, and Ghislaine van Mastrigt.

Thank you for reviewing our manuscript. We carefully considered all comments made by the reviewers and revised our manuscript accordingly. To the best of our capacity, we made textual adjustments throughout the entire manuscript according to the provided minor revisions. Following the suggestions for major revisions, table 1 presents the way we handled these suggestions.

All authors have read and approved the revised manuscript; the manuscript has not been submitted elsewhere nor published elsewhere in whole or in part, except as an abstract.

If accepted, the manuscript will not be published elsewhere, including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder.

We hope that you are willing to consider the publication of our manuscript in BMC Neurology.

Yours sincerely, on behalf of all authors,

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Dear reviewers, thank you very much for reviewing our paper, we have tried to answer all queries as good as possible. We think our paper has really improved by your suggestions.

Post-stroke depressive symptoms occur frequently in the chronic phase after stroke [5-9]. Recent data from the National Stroke Association show that approximately one-third of stroke survivors is affected by varying degrees of post-stroke depression amongst other symptoms [10]. In addition, these symptoms often coincide with increased feelings of anxiety [11]. Besides the major impact on health-related quality of life (HRQoL) [12], post-stroke depressive symptoms are associated with increased hospitalization and therefore substantial healthcare costs [13].

Previous research has evaluated different interventions focusing on the treatment of post-stroke depressive symptoms, such as pharmacological interventions [16, 17], yet evidence for the effectiveness of stroke-specific psychological interventions is limited [18]. This is, mainly related due to possible lack of efficacy of the interventions under investigation, but also caused by poor study design [19].

Furthermore, the characteristics of CBT seem to suggest it ought to be an especially good fit to meet the needs of people who suffer from post-stroke depression [17]. Depressed stroke survivors endorse significantly more negative conditions than non-depressed stroke survivors [30, 31]. In addition, there is good evidence that remaining active, expressing emotion and finding positive meaning ensures good psychological adjustment in other chronic illnesses [32].

The time horizon of eight months was chosen because we expect possible differences between both interventions to appear within this time frame. Finally, we found and measured differences between interventions within the time horizon, by adding extra follow-up measurement moments or using modelling techniques in further research in order to identify the long-term effects of both interventions in comparison to each other.

As presented in figure 1, the percentage of missing data at T1 was 15% (n=9), at T2 was 21% (n=13) and at T3 was 28% (n=17). Next, we had to deal with a considerable number of missing data.
Authors justify their approach? Could the sensitivity HC may have overestimated costs. Could the authors give more comment on the impact of the outcomes measured either here or the discussion section?

Line 250: How was cost effectiveness defined? Or more specifically, what was considered to be a successful ICER? This is a very valid and relevant question, causing much debate under health economists and researchers as well. We explained our view and thoughts in the methods sections of this manuscript. However, we agree that the interpretation of an ICER must be done with care and is very dependant on the level of willingness to pay. Since there are no guidelines (or consensus) on the willingness to pay level of the HADS, careful interpretation is advised. A CEAC shows the probability of an intervention to be a cost-effective alternative for a certain threshold; the amount of money society is willing to pay (WTP) to gain one unit of effect (e.g. a one-point improvement on the HADS or one QALY). For the HADS, the WTP threshold is an unknown quantity. A previous study on manual psychological therapy for dementia patients used a WTP level of €500 per one-point improvement on the HADS [52]. The minimal important difference of the HADS has not been established, but in patients with chronic obstructive pulmonary disease (COPD) a minimal important difference of 1.6 was found [53]. The WTP threshold for a QALY differs per country or even within countries. In the Netherlands, the Dutch Council of Public Health and Care published a report in 2006 regarding the burden of disease in the Netherlands, estimating a QALY threshold for stroke at €40,000 Euros [54].

Line 277: Friction method needs more description. I noted the authors used a human capital approach (line 230) I presume productivity cost were calculated up to 65 years of age? If so I would argue that a friction cost method should have been used within the base case analysis instead (Human capital (HC) in the sensitivity HC may have overestimated costs. Could the authors justify their approach?

Thank you for this very interesting thought. After careful consideration we chose the human capital approach for our base case analyses. Mainly because this is the international standard of calculating productivity costs and the friction cost method is subject to variety in the national economic cycles. We provided more detail information on our arguments in the methods section of the manuscript, as well as supporting references.

Productivity costs were valued according to the human capital approach. This approach states that productivity costs are calculated by multiplying the number of sick days by the costs of labour, corrected for different age categories. The human capital approach is the international standard in calculating productivity costs, whereas its counterpart, the friction cost method, is subject to variety in the national economic cycles [46, 47]. Furthermore, due to changes in Dutch legislations, it is unlikely for employees that they are being replaced, making it imperative to include long-term absenteeism as well.

Line 294 What are the possible reasons which might explain the difference in societal costs between groups? We agree with this suggestion. We provided more detailed information on the explanation of cost differences in the discussion section of this manuscript. Especially hospital admission, specialist consultations, home adjustments and productivity costs were responsible for major differences. However, since the study population was small, these differences must be interpreted with caution. Line 377-383

Cost differences between the two groups could be explained by costs of admission to a hospital, specialist consultations and home adjustments, but the larger part of the difference in total costs was due to productivity costs of both the patient and the caregiver which were both significantly lower in the augmented CBT group. The fact that, at baseline, 43.3% of the control group had paid work, in comparison with only 29% of the augmented CBT group, and that patients in the control group worked more than twice the number of hours per week might explain this difference.

Line 319 Author could state the ICUR resulted in cost savings (i.e., €160.390)? Rather than a “negative ICER”. Could the authors give more comment on the impact of the outcomes measured either here or the discussion section?

We agree with this point, interpretation of a negative ICER is difficult, confusing and might lead to misinterpretations. Therefore, we reformulated some lines to explain these results better. Line 336-338 and 387-388

As we explained in the discussion section of the manuscript, the outcomes show potential of the CBT intervention to be a cost-effective alternative. However, due to limitations (e.g. small sample size) and patients in the augmented CBT group gained slightly more QALYs (mean: 0.01) compared to control group patients. More QALYs gained combined with fewer societal costs (+€1,913) induced by the augmented CBT group resulted in a dominant ICER.

A dominant ICER for the QALY was found, indicating higher effects and fewer costs for the augmented CBT group.
an ‘active’ control group, the impact of the outcomes measures must be interpreted with care. We think that the suggestions based on our outcomes presented in our manuscript, provide clear directions for future research.

### Line 335
Although the sensitivity results echo common and known trend, for instance lower costs depending on perspective and productivity cost methods. Should the HADS (rather than QALY) being tested also in the sensitivity analysis?

This is a very interesting thought, which led to discussion amongst the authors. After careful consideration we chose not to test the HADS subdomains (HADS-D and HADS-A) in a sensitivity analysis. On forehand, we decided to use the HADS-T instead of HADS-D and HADS-A. In addition, the cost-effectiveness manuscript is attached to and unpublished (yet) effectiveness article, reporting on the HADS-D and HADS-A.

### What are the “next steps” or recommendations for further research?
Thank you for this suggestion. We provided some more information on recommendation for further research. We agree with you and we think that this is an important section in our manuscript. Line 441-445 and 450-455

Finally, we found and measured differences between interventions within the time horizon chosen for this study. However, with progressing insight, we would argue that it would be interesting to expand the time horizon, by adding extra follow-up measurement moments or using modelling techniques in further research in order to identify the long-term effects of both interventions in comparison to each other.

However, other studies showed the potential for the augmented CBT intervention to be cost-effective in treating depression. Although we have argued why we have chosen an ‘active’ control intervention, it would be very interesting to investigate the effect of including a care as usual group as third study arm in future research. Therefore, for further research we would recommend recruitment of a larger stroke population, i.e. in multiple sites.

### Line 401-404
Why was cogniPlus chosen as the comparator? And care as usual omitted from the analysis?
This is a very relevant question, which deserves more attention in our manuscript. This suggestion is in line with a previous comment on the provision of more information on both programs. The major reason for choosing CogniPlus as control intervention lies in previous evidence, which is now explained and provided in the methods section of our manuscript. Line 169-174

We chose to compare the augmented CBT intervention to an ‘active’ intervention (and not usual care) to control for Hawthorne effects. Evidence from Spikman et al. [36] showed that a similar control group did not improve in executive functioning, and that generalisation of what was assessed in the control intervention to daily life did not occur. Further information on the justification of both interventions can be found elsewhere [15, 34].

### Line 418:
With the number of missing values for HADs and EQ-5D-3L. Should a feasibility study be carried out to investigate whether data collecting methods is capable of obtaining these outcomes? Or something else?
This is a very interesting thought provided by the reviewer, thank you for this suggestion. We discussed this topic, but concluded (after considering previous study results) that we do not think that the feasibility of the HADS and EQ-5D-3L is the reason for missing values. The major reason for missing values is related to the fact that we should have paid more attention in the follow-up period of this study to avoid early withdrawal and dropout.

The author states that further research in a larger population is needed. Could they please provide more description here?
Thank you for this suggestion. We agree that we should have addressed this subject with more information. As we recommend the possibility of a third study arm (usual care) in future research, we argued that a larger population is recommended. Line 450-455

However, other studies showed the potential for the augmented CBT intervention to be cost-effective in treating depression. Although we have argued why we have chosen an ‘active’ control intervention, it would be very interesting to investigate the effect of including a care as usual group as third study arm in future research. Therefore, for further research we would recommend recruitment of a larger stroke population, i.e.
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<th>in multiple sites.</th>
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<td>Further description of the two programs compared in this economic evaluation is needed.</td>
<td>Thank you for this suggestion, we agree that it is relevant to provide enough information on both programs for readers to understand the contents and differences. We provided more information on both programs in the methods section of this manuscript, as well as two references for more detailed information. Line 169-174</td>
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<td>We chose to compare the augmented CBT intervention to an 'active' intervention (and not usual care) to control for Hawthorne effects. Evidence from Spikman et al. [36] showed that a similar control group did not improve in executive functioning, and that generalisation of what was assessed in the control intervention to daily life did not occur. Further information on the justification of both interventions can be found elsewhere [15, 34].</td>
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