Reviewer’s report

Title: A Personalized Intervention to Prevent Depression in Primary Care: Cost-effectiveness Study Nested into a Clustered Randomized Trial

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Reviewer: Christian Brettschneider

Reviewer's report:

The manuscript „A Personalized Intervention to Prevent Depression in Primary Care: Cost-effectiveness Study Nested into a Clustered Randomized Trial” addresses an important and interesting topic, the prevention of depressive episodes by a personalized approach. In general, the paper is well written and all relevant aspects are presented. The design of the economic evaluation conforms to the international standards of a state-of-the-art analysis. The authors report the ICER, the CE-plane and the CEAC. The statistical analysis considers thoroughly the specific distributional characteristics of cost data. The authors perform different GLM and evaluate the quality of the models. Finally, the authors decide to use GLM with gamma-log for costs and gaussian-identity for QALY. Based on experience from previous analyses, this appears to me as a suitable and appropriate choice. The results section is well structured and comprehensive. The discussion section presents the most important result, discusses strength and limitations and shows implications for practice. The conclusions are supported by the results. This is the second economic evaluation of an intervention based on the PredictD risk algorithm. The personalized intervention is an innovative aspect. Hence, the manuscript represents a progress.

Apart from the positive aspects mentioned above, there are some concern I have related to the manuscript, especially in context with the analytical approach.

In the Introduction, the authors stress the point that primary prevention is the most important approach to reduce the incidence of depression and it seems to me from the content of the analysis that the authors see their intervention as primary prevention. However, in the first paragraph of the result section the authors declare that the number of patients with a previous episode of depression was higher in the intervention group. Hence, the study considers participants unaffected by depression and those affected by depression. It is not clear to me if and I am in doubt that the mechanisms of the intervention are the same for people without previous episodes and those with previous episodes. Based on the logic of prevention the first group is a target group of primary prevention and the second group is a target group of tertiary prevention or maintenance of remission. Both prevention types use different instruments and have other objectives, so it is probable that the intervention has different implication in both groups. To receive a clearer and more robust picture of the true cost-effectiveness of the
intervention, I want to ask the authors to perform subgroup analyses for participants without prior episodes and for those patients with previous episodes. Additionally the authors should make clearer which approach to prevention they foster with their intervention.

Related to the statistical analyses, I have two specific concerns that need to be addressed by the authors. Firstly, the authors write that the participants in the intervention group had a higher risk of depression than their counterparts in the control group. As discussed by the authors, imbalances can appear because of the cluster-randomization. However, this specific imbalance is quite problematic as it is directly connected to the aim of the study. Patients with a higher risk of depression receive an intervention to prevent depressive episodes. This group has better chances to show improvements. It is essential to consider this aspect in the statistical analysis, either by controlling for this risk or by matching/balancing the groups. Secondly, the authors recruited patients, treated by different physicians, working at different primary care centers, which were located in different cities. This is a high number of clusters. The authors control for some of these effects but not for all, e.g. city. At least the authors have to confirm that this is not necessary.

Concerning the level of the economic evaluation, I have one concern that the authors should consider. The authors calculated ICER based on adjusted costs and QALY. This is not proper without further adjustments. If the authors want to present such an adjusted ICER, they have to perform a Cholesky decomposition (or a comparable approach). Otherwise, the authors should present and discuss the unadjusted ICER and draw their conclusions from the CEAC.

There are further minor aspects the authors should correct.

- How did the research assistants randomly select the patients?

- The authors should give at least a short description of the components of the PredictD-algorithm.

- The authors should cite a source for the unit costs for the calculation of the indirect costs.

- Presenteeism costs were calculated. The authors should give some information on the assessment and valuation.

- The authors should state that the analyses were performed based on the ITT principle.
- There is no description of the calculation and construction of the CEAC (NBR approach). This should be changed.

- In table 2, the upper limits of the CI for the QALY differences are different between societal and National Health perspective.

- The authors should discuss that they did not consider costs for informal care and general medication. Both are relevant categories. The authors said that the patients in the intervention group had a different perception of safety inside-outside the home. These patients are prone to use supportive services delivered by relatives. On the other hand, has depression an influence on somatic health too. On this way, it influences the utilization of medication in general.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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