Author’s response to reviews

Title: Effectiveness of diabetes self-management education via a smartphone application in insulin treated type 2 diabetes patients. Design of a randomised controlled trial (‘TRIGGER study’).

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Response letter to reviewers’ comments - BEND-D-17-00313

"Effectiveness of diabetes self-management education via a smartphone application in insulin treated type 2 diabetes patients. Design of a randomised controlled trial (‘TRIGGER study’)"

Reviewer 1 - Astrid Torbjornsen

1. Consider to delete the "(cost)" in the aims as HbA1c is primary outcome and cost only part of the secondary outcomes.

In both the Abstract, page 3, line 42 and in the Methods section, page 8, line 152 we have deleted "(cost)"

2. Consider to make clear that you wrote the background according to study start in 2015, or add an update as there are a considerably amount of relevant evidence from the years after 2015.

We have updated the background section by including the following studies:

- A study to illustrate the rapid increase in the number of diabetes apps (Martinez-Perez et al. 2013; background, page 5, line 96)
- A recent meta-analysis as a reference to the effectiveness of apps (Hou et al. 2018; background, page 6, line 103, 106, 107)

- A systematic review which supports our statement on the limitations of the current evidence, i.e. small sample sizes, feasibility studies, short duration (Wang et al. 2018; background, page 7, line 142)

- An overview of systematic reviews as a reference to the effectiveness of apps (Byambasuren et al. 2018; page 6, line 107) and to support our statement on the limitations of the current evidence (Byambasuren et al. 2018; background, page 7, line 142)

3. There is an inconsequence in the manuscript due to presentation of HbA1c level between >53 mmol/mol (>7%) and the opposite ≤7% (≤53 mmol/mol). A consequent order would ease the reading.

Thank you for pointing this out. We have changed the order to mmol/mol - % in the Methods section, page 14, line 291.

4. The manuscript does not describe demographic and clinical variables other than randomly. As an example, do the variables include socio-economic status and frequency of attending health services mentioned in the discussion?

We added the following to the Methods section, page 15, line 315: “In addition to anthropometric (length, weight, waist circumference and blood pressure) and laboratory parameters (HbA1c and lipid profile), the following demographic and clinical variables were collected: age, duration of diabetes, ethnicity, level of education, smoking status (current, former, never), presence of microvascular complications (nephropathy, retinopathy, neuropathy) and macrovascular complications (cardiovascular diseases), and diabetes medication use (including insulin injection frequency and dose)”. And further, line 322: “For the cost-effectiveness analysis, data on health care use are extracted from both the electronic medical record and from the questionnaires sent to the participants at T3 and T6.”

5. Please explain why the T9 follow-up does not include the control group, as the measurement is relevant for all three groups (continuers, discontinuers and control).

Since our primary outcome is measured at T6, and our sample size is calculated on this, a comparison at T9 could quickly become underpowered. Moreover, because at T6 the intervention group could choose whether or not they want to continue the intervention, (unmeasured) confounding can be an issue at T9; by including a control group, readers could easily misinterpret the results at T9.
6. It is not clear what discontinued use of the app after 6 months means, is it the patients that did not actively prolong the intervention, or in addition those who prolonged, but did not read the messages?

We edited the text and now explained prolonged use versus discontinued use as follows: “The latter is investigated in the intervention group only: we will compare the effect of three months prolonged use of the app to stopping with the use of the app, on HbA1c, on the percentage of patients who achieve an HbA1c level ≤53 mmol/mol (≤7%) without any hypoglycaemic event, BMI, and health status. Prolonged users are individuals from the intervention group who choose to continue the intervention after six months (T6); discontinued users are those who do not continue using the app after T6.” (Methods section, page 14, line 298).

7. Line 280 and 281 describe, "The messages do not contain any personal information and logging data are anonymized". Still, some of the messages indicates that the receiver possibly may have hypoglycemic events and uses insulin. The manuscript presents the messages as unidirectional; please elaborate what the logging data refers to - the app messages, the push messages or other? How are they anonymized?

Logging data refer to (1) successful delivery of the (pre-announcement of the) push-message and (2) delivery of fall-back SMSs. The logging data are anonymized by separating these from the personal data. We’ve changed the sentence in the Methods section, page 14, line 285 to: “The logging data, such as successful delivery of messages, are anonymised by separating them from the personal data.”

8. The participants receive patient diaries at the start of the study. Is this a traditionally paper diary, or is it digital, integrated in the app and part of the log data?

In the study we use a traditional paper diary. Because the control group will not use an app, we choose not to provide a digital diary, since we wanted the assess the number of hypoglycaemic events uniformly. We have added “paper” to diary to the Methods section, page 11, line 228.

9. In the discussion, use of other apps is a theme. This is interesting and use of other apps can contaminate the findings. The manuscript argue that both the intervention and the control group are able to use other diabetes apps, but there is a risk for developing differences between the groups due to the nature of the study. It would be interesting to read some further discussion due to this issue. Does the study survey use of other apps?

Unfortunately, we do no register participants’ use of other apps. Since the inclusion already started in 2015, we are not able to integrate this. It is however a valid point you raise here, which we might use in the discussion of our future result paper.

10. In Table 3, all the references are offset (wrong numbers).
Thank you for raising this issue. We have changed and checked all references.

11. The questionnaire "Satisfaction and usability of the app" is a newly developed questionnaire and lack a reference. Do the researchers develop the questionnaire for this particular study? It will be interesting to read the authors reflections of their choices due to the few validated app satisfaction questionnaires.

We did develop the questionnaire ourselves, to make this more clear we have changed the text in Table 3, page 34 to: “Questionnaire newly developed by the researchers”. Initially, we wanted to include a validated questionnaire, but unfortunately we were not able to find an appropriate one back in 2015. We have included a translation of the questionnaire as an appendix to the manuscript. The original Dutch questionnaire has been translated via a forward-backward procedure.

12. Consider to turn Figure 1 as it is less intuitive to read a flowchart from the bottom.

We turned Figure 1:

Reviewer 2- Elaine Lum

1. Background section: Line 98-99 requires a reference (sentence ending with "... but apps facilitating these features are associated with higher costs").

We changed this sentence: "but apps facilitating these features are likely to be associated with higher costs”, see Background section, page 6, line 105.

2. Background section: Line 102 (and the corresponding paragraph): A new paper has just been published which the authors may wish to include. Byambasuren O, Sanders S, Beller E, Glasziou P. Prescribable mHealth apps identified from an overview of systematic reviews. npj Digital Medicine 1, Article number:12 (2018). Available from: https://www.nature.com/articles/s41746-018-0021-9

Thank you for pointing out this interesting article. We have included this overview of systematic reviews as a reference to the effectiveness of apps (Byambasuren et al. 2018; page 6, line 107) and to support our statement on the limitations of the current evidence (Byambasuren et al. 2018; background, page 7, line 142).

3. Methods section: Line 265-268. May be useful to survey patients in both the intervention and control arms at baseline (T0) and at the conclusion of the study (T6) regarding their use of other health apps relevant to this study (e.g. physical activity apps, diet/nutrition apps, weight management apps, blood glucose monitoring apps, etc).
Unfortunately, we do no register participants’ use of other apps. Since the inclusion already started in 2015, we are not able to integrate this. It is however a valid point you raise here, which we might use in the discussion of our future result paper.

4. Methods section: Line 293-294. For comparison of the intervention sub-groups at T9 between those who continued using the app and those who did not, why not include also the co-primary outcome of the proportion of patients achieving desired HbA1c without hypoglycaemia, and the number of hypoglycaemic episodes, as you would have collected this data anyway (patient diaries up to T9 was mentioned in Line 311). This would give us some interesting insights as to the sustainability of the intervention effect in regards to avoiding hypoglycaemia.

We have added this outcome, Methods section, page 14, line 300.

5. Cost-effectiveness analysis: I note that the cost-effectiveness analysis will only be carried out if the intervention is successful in delivering desired outcomes. Is it possible to also include ICER? The CEAC will only present the probability that the intervention is cost-effective.

Thank you for pointing this out, we did not write this down correctly and have changed the text in the Methods section, page 17, line 370 to “The cost-effectiveness of the intervention …”.

In fact, we are performing an ICER, but a special type of ICER, namely a cost utility analysis. In this analysis the costs are related to a generic health outcome (QALYs); by doing so, results can be compared over different diseases. We purposely did not write “ICER” because this can have different meanings; we therefore decided to report cost data and effectiveness data separately.

6. Table 1 has 2 inconsistencies. Intervention row - Patients choose 3-4 topics, including hypoglycaemia; but in the manuscript this was stated as 2-3 topics, including hypoglycaemia. Key secondary outcomes row - body weight is mentioned explicitly here, but not explicitly mentioned in the manuscript (implied via BMI only).

In the trial registry we have written the following:
- Patients choose their preferred frequency and topics of the text message (3 or 4 topics, including at least hypoglycaemia)

In the manuscript we have written the following:
- hypoglycaemia will be a mandatory topic, it should be combined with at least two of the following topics: dietary habits, physical activity or glucose regulation (including glycaemic variability).
These are indeed different phrasings, but both describe the same, i.e. hypoglycaemia is a mandatory topic, combined with 2-3 extra topics, which will result in 3-4 topics in total.

With regard to body weight and BMI, we have indeed listed both in the trial register. We now also listed weight as an outcome in the Methods section on page 14, line 293.