Author’s response to reviews

Title: A virtual clinic for the management of diabetes-type 1: Study protocol for a randomised wait-list controlled clinical trial.

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Author’s response to reviews:

Dear Editor

We are pleased to submit our revised study protocol ‘A virtual clinic for the management of diabetes-type 1: Study protocol for a randomised wait-list controlled clinical trial’ BEND-D-20-00044 for consideration for publication in BMC Endocrine Disorders.

We are grateful to the Editor and to the Reviewers for the constructive and thoughtful critique of our study protocol. Please see below for a detailed point-by-point author response to each comment with specific notations of the manuscript changes. We believe that the peer review process has greatly enhanced our manuscript and hope that it is now acceptable for publication in BMC Endocrine Disorders.

Sincerely,
Elisabet Nerpin PhD

Reviewer 1:
This is an important study exploring the effect of a virtual clinic for an important and poorly controlled group of people with type 1 diabetes. This is a protocol paper, so it describes the methodology for a study that has already been peer reviewed and funded, and which I presume has ethical approval.

I have some minor but important comments and reflections on the study design and write up
1. The duration of type 1 diabetes needs to be clarified in the methodology and the researchers need to consider whether they restrict recruitment to people after 5 years of diagnosis. This is because HbA1c is generally not stable over the first 5 years. Therefore, the natural history of the disease, rather than the intervention, may account for any changes seen during the study. See Krishnarajah et al 2018 article on glycaemic tracking also replicated with data from Scottish database.

Authors’ response: Thank you for an important question. Due to the benefit of the research design, randomization: it eliminates the selection bias, balances the groups with respect to many known and unknown confounding or prognostic variables, and forms the basis for statistical tests, a basis for an assumption of free statistical test of the equality of treatments. We have added following to the method section, line 15-17, page 5:

Exclusion criteria are: duration of diabetes shorter than 1 year, a diagnosis of severe depression; eating disorders or other serious mental illness; alcohol/drug abuse; or severe diabetes complications.

2. It is not clear why a standard cross over design is not used. Instead one arm stays on the intervention during the second 6 months. Additional statistical power may be obtained if the treatment arm reverts to the usual care arm. Some explanation as to the thinking behind this would be useful.

Authors’ response: We prefer a wait-list control group design, as more patients can be offered the same intervention or treatment as those in the experimental group but at a later time.

3. Data needs to be collected on those participants who refuse to enter the study. These may be the patients who need most support with their diabetes control.

Authors’ response: We agree, but due to the ethical applications it was impossible to perform.

4. Please clarify if data is being collected for health economics - if the study is shown to be effective then it would be important to show that it is also cost effective.

Thank you for a good suggestion.

Authors’ response: We agree with the Reviewer that health economics is important. However, the focus of this study is not on health economy. Perhaps, in an upcoming larger study, we will consider your proposal.

5. Whilst time in range data is collected, please also ensure that rates of DKA and severe hypo are collected.

Authors’ response: We thank the Reviewer for the relevant and constructive comments. Severe Hypoglycemia and Diabetic Ketoacidosis is very important for this age group. We have this data in the patient’s journal. We are going to collect this data.

We have added following to the Method, line 26-27, page 5:
The primary outcome/end point will be glycaemic control; HbA1c, Time In Range and Time Below Range, Severe Hypoglycemia and Diabetic Ketoacidosis, respectively.

6. There are some minor typographical errors which require correcting

Author response: We thank the Reviewer for the careful inspection of our manuscript. We have carefully review paper for typos and awkward wording.

Reviewer 2:

This is a protocol review aimed at assessing the efficacy of a virtual clinic for people with type 1 diabetes. The methods appear to be appropriate given that this is only a protocol study but would benefit from the following:

In the introduction, the authors provided some rationale on the efficacy of telemedicine and the reasons for assessing this in type 1 diabetes. However, there are some nuances in this as follows:

1. The intervention is poorly described. While the aim is to improve diabetes self-efficacy, there is nothing much described on what the intervention comprised of except that it is as stated a virtual clinic. Studies and reviews by several groups have shown that there are many different definitions to telemedicine. Please see this Distal technologies and type 1 diabetes management. DOI: 10.1016/s2213-8587(17)30260-7, Danny C Duke, Samantha Barry, David V Wagner, Jane Speight, Pratik Choudhary, Michael A Harris Lee, S.W.H., Chan, C.K.Y., Chua, S.S. and Chaiyakunapruk, N., 2017. Comparative effectiveness of telemedicine strategies on type 2 diabetes management: a systematic review and network meta-analysis. Scientific reports, 7(1), pp.1-11.

Author response: We are grateful for the valuable references and the one by Duke et al is now included in the manuscript. We have added some examples about possible reasons for suboptimal glycemic control in this age-group (Background, line 11-15, page 4):

In another review focusing on type 1 diabetes and distal technologies (various electronic systems providing remote services) telehealth, such as telephone calls and video appointments, was the one technology that hitherto could prove similar or better glycaemic control with potential additional benefits, regarding costs, efficiency geographic barriers and convenience.

2. It would be important that the authors describe in detail how and what the intervention includes. Does it only involve providing a platform to ensure continuity of care which is already implemented in many countries, either through a diabetic nurse or case manager? Or does it have additional functions like monitoring, education etc?
Author response: This is an important comment and the manuscript has been supplemented with information about the function and design of the virtual clinic. Using the definitions stated by Duke et al in the reference above the intervention can best be described as a combination of a telehealth system for communication via text messages or video appointments and a patient portal where the patient can for example book virtual appointments or make prescription requests. It is also possible for both patient and caregiver to upload documents or photos. Hopefully, these additions have significantly improved the clarity and quality of the manuscript. We have added some clarity to the script (Method, line 7-16 page 7):

It is also possible to start a spontaneous video meeting if a need arises in connection to a text message chat between patient and nurse. Documents or photos can easily be shared by patient or caregiver in the platform. Data from proximal technology (insulin pumps and CGM) is uploaded by the patient and can be reviewed and discussed in collaboration. Patients and caregiver have simultaneous access to data in platforms such as Diasend® or CareLink®. All together this invites and enables the patient to put forward their needs in the moment they arise. That contrasts to the conventional clinic where the patient needs to wait for a telephone consultation or the booked consultation in the future. Participants are well informed that the virtual clinic is not intended for very acute cases, such as ketoacidosis, and that the caregiver is only available during daytime weekdays.

3. Can physicians or nurses adjust any medication dosage?

Author response: At the virtual meetings, which can be initiated either by the nurse or the doctor or by the patient, a change in the insulin dose may be recommended. The change in dosage is always discussed and motivated in collaboration with the patient in order to increase the self-care in the longer run.

4. The sample size appears to be relatively small to be sufficiently powered to show any real changes. Multiple reviews published to date have shown that most studies are underpowered to show any statistical significance or even clinical significance as 6 mmol/mol is a really small change in HbA1c so i am questioning the significance to patients and clinicians.

Author response: Although difference in HbA1c is traditionally the primary outcome measure in studies of diabetes treatment, this outcome is supplemented by measures of time in and outside the glycemic range (TIR). Since the majority of patients in the target group use some form of continuous glucose monitor (CGM) and time in range (TIR) will be available for evaluation. TIR is easier for the patient to understand and self-evaluate, compared to HbA1c. This is encouraged and discussed in the virtual contact. We believe the clinical significance of the study may be enhanced by other measures of glycemic control than HbA1c, such as TIR, but that HbA1c should be included as a traditional measure. The power calculation is carried out based on what is generally considered significant regarding the risk of complications.

5. Some minor typo changes and errors in the title.
A virtual clinic for the management of diabetes-type 1: Study protocol for a randomised wait-list controlled clinical trial.

6. Perhaps the authors should check and cite newer studies as there are newer GBD studies than those cited in 2016.

Author response: We are thankful to this comment and have replaced the reference with a more recent one (Background, line 3, page 3).

Reviewer 3:

This manuscript describes the protocol for a randomized wait-list controlled clinical trial to evaluate the effect of a virtual diabetes clinic on glycemic control, treatment satisfaction, quality of life, and patient care experience in young adults (ages 18-25) with type 1 diabetes. Strengths of the manuscript include outlining a feasible RCT study design and addressing a gap in the literature surrounding the assessment of patient-centered virtual diabetes care, especially for young adult patients. Although an important and relevant topic, more detailed information is needed in the current manuscript. Following are points of consideration:

Background:
1. The authors describe how young adults are particularly vulnerable to suboptimal glycemic control, but don't include any specific examples or speculate why this might be. The paper would benefit from discussion of some of the major developmental milestones and challenges that young adults face as they relate to glycemic outcomes.

Author response: We have added some examples about possible reasons for suboptimal glycemic control in this age-group (Background, line 15-20, page 3).

The reason for this is partly unknown; factors such as genetic variations, fear of hypoglycemia, stress, depression, and lack of knowledge may be contributing factors. In addition, studies have shown that depression is two to four times more common in people with diabetes compared with the general population. The self-management is often unsatisfied with many missed doses to meals and snacks.

2. It would be helpful to the reader to provide more concrete examples and citations of why virtual diabetes clinics would be useful in supporting diabetes management in the last paragraph of the background section.

Author response: We agree with the Reviewer and we have added the following sentence (Background, line 26-28, page 4):
Virtual clinics increase the opportunities for people with diabetes to retain contact with” their” diabetes nurse or doctor, allowing for continuity of care and providing a sense of security for many patients.

3. The authors state that "...the technological developments in diabetes care have placed higher demands on education and support," which contradicts the overall argument that virtual diabetes care (a technological development) can help to improve management. Please clarify this on page 3.

Author response: We have added an explanation: (Background, line 22-23 page 4)

At the same time, they frequently have advanced technologies (e.g. insulin pumps and flash glucose monitoring systems), which provide in-depth data, able to share on-line with health care professionals, allowing detailed analysis and advice for diabetes care at a distance.

Method/Design:

4. Please include rationale for exclusion criteria of severe depression, eating disorders, serious mental illness, alcohol/drug abuse, or severe diabetes complications- several of which are not uncommon in this young adult population with T1D. Please also describe how these will be assessed in order to exclude.

Author response: We thank the Reviewer for the relevant and constructive comments. The diabetes nurse and/or the doctor will be the person who makes the decision whether the diabetes patient has the compliance to be able to participate in the study. We have clarified our exclusion criteria section with (Method, line 15-19, page 5)

Exclusion criteria are: duration of diabetes shorter than 1 year, a diagnosis of severe depression; eating disorders or other serious mental illness; alcohol/drug abuse; or severe diabetes complications. The diabetes nurse and/or physician will be the person who makes the decision whether the diabetic patient has compliance to be able to participate in the study.

5. It would be helpful to include whether or not duration of diagnosis will be used as inclusion criteria. The authors should consider excluding participants with duration less than 1 year- honeymoon is often continued through one year and patients are still adjusting through the one-year period.

Author response: In the inclusion of the study subjects, we will take into account how long they have had their diabetes. However, data is collected regarding diabetes duration. This gives us the opportunity to take into account duration both by being able to adjust and create groups in terms of duration.

We have added the following text to our manuscript (Method, line 15-16, page 5):

Exclusion criteria are: duration of diabetes shorter than 1 year
6. The author states that "hospital staff in the clinic (doctors and nurses) will be responsible for the inclusion, randomization and the interviews," but concerns about experimenter bias should be raised, as these staff are also providing direct care for the patient.

Author response: No hospital staff have been involved in the preparation of the closed randomization cards. We have added the following text to our manuscript (Method section, line 33, page 5 and line 1-2 page 6):

The closed envelopes have been developed by a person who is not involved in the inclusion or care of the patients.

7. As these participants will still be receiving their "usual diabetes care," what role does the smartphone application play? Please provide more information about how this app is used as a supplementary tool (e.g. does it include information about nutrition, exercise, etc.) to usual diabetes care.

Author response: We have added a more detailed explanation about the virtual care (Method section, Line 26-34, page 6):

Vista Dialog supports a way of working that allows more frequent communication when needed, whilst allowing continuity of care and minimal disturbance to daily life. It provides additional access to healthcare without over-burdening health care professionals. For users, the virtual care increases the feeling of being in control and is easy to use and understand. The ability to provide instantaneous feedback means a more effective evaluation of health care interventions is possible. The simple method of facilitating further discussion contributes to an increased participation in the care which means that any potential problems or obstacles are discovered more quickly. Vista Dialog complements the usual care at the outpatient clinic and other eHealth services.

8. Please report use of diabetes technology including meter use, insulin pumps, and CGMs. Further, differences in technology may impact participants' ability to interact with the application and should be included in analyses. Will patients who are not using CGM be excluded from participating?

Author response: A majority (93%) of patients have either CGM or FGM. In addition, those who don’t use these systems can download capillary measured blood glucose.

9. Please provide information on race and ethnicity in addition to the report of Swedish nationality. Relative lack of heterogeneity should also be included as a study limitation.

Author response: We appreciate this suggestion from the Reviewer and have addressed this the following way (Discussion, line 12-14 page 11):
In Sweden, patients with T1DM are only treated at specialist centres and no concomitant care is involved in the diabetes treatment, and all patients at the clinic who fulfil the inclusion criteria can be enrolled, regardless race and ethnicity.

10. It is unclear why insulin requirements/dosages will be used as an indicator of glycemic control, please provide more information and/or citations.

Author response: We have added information and a citation about this (Method, line 27, page 7).

Insulin requirements/dosage to explore changes as a further indicator of glycaemic control, as missed doses are common

11. A more appropriate title for "Clinical Outcome Measures" may be "Clinical Variables," as not all that are listed here are "outcomes" (e.g. diabetes duration is not an outcome).

Author response: We have changed according to your suggestion.

12. Under Psychometric Measures, we suggest "health and quality of life" be replaced with the measure name "Check Your Health"

Author response: We have changed according to your suggestion.

13. It would be helpful to know how the surveys are administered (e.g. in-person or online).

Author response: We have clarified manuscript how the surveys are administrated. We have added the following information (Method, line 7-8, page 8)

All data will be collected in-person at the diabetes clinic (clinical variables and psychometric measures).

14. The qualitative interview may be a good opportunity to ask about specific aspects of the app that were helpful/not helpful to the participant, in addition to a broader perception about virtual care.

Author response: Thank you for a good suggestion to improve our interview guide We have added one question to our interview guide (Method, line 23-25, page 9)

´Can you describe how you used the application (app) in your daily life and specific aspects of the app that were helpful/not helpful for you´

Discussion:
15. Please discuss potential limitations and risk of study.

Author response: We agree with the Reviewer that we can discuss some limitations to the script. We will also discuss in more detail our strengths and weaknesses that we are aware of when we
are going to present our results. We have added some limitation to our discussion, (Discussion, line 23-29, page 11)

Study limitations
We can see some limitations for our study. First, we only include patients from one clinic which may limit the generalizability. The admission area for the study hospital comprises an entire county and thus includes patients with a mixed socio-economic background, which increases the external validity. Secondary, young adults can be a difficult age group to include. However, the clinic is responsible for approximately 400 young adults with type 1 diabetes, so we do not think that this will affect our inclusion to the study.

Miscellaneous:
16. Authors should carefully review paper for typos and awkward wording (e.g. page 3, sentence beginning with "To achieve optimal self-management…"; page 5 line 16 "collect data t"; page 6 lines 15-16 "continuos glucos").

Author response: We thank the Reviewer for the careful inspection of our manuscript. We have carefully review paper for typos and awkward wording.