PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Dietary Education Trial in Carbohydrate Counting (DIET-CARB Study): study protocol for a randomized, parallel, open-label, intervention study comparing different approaches to dietary self-management in patients with type 1 diabetes
AUTHORS	Ewers, Bettina; Vilsboell, Tina; Andersen, Henrik; Bruun, Jens

VERSION 1 – REVIEW

REVIEWER	Nicole Farmer National Institutes of Health Clinical Center
REVIEW RETURNED	11-Apr-2019

GENERAL COMMENTS	I highly recommend accepting this manuscript for publication. It is relevant for type 1 diabetes care and also provides a relevant and very well designed example of testing an clinically relevant experience based intervention in a medical clinic setting. My only comments for the authors are that the introduction gives the impression that the analysis will give not only BCC and ACC to usual dietary guidelines, but also BCC to ACC. I was glad to see the power analysis was for the former and not the later. The authors state that a limitation is lack of a dietary untreated control group. I would agree but present that having this control group may go against standard of care for type 1 diabetics, and thus having it as a randomized group may insert ethical issues. I think there is another limitation present which the authors may consider when reviewing their results. The BCC group has group modeling and more group time than the ACC or the control group. Group effects of modeling, experiential learning from others may play a part in any intervention effect, as much as acquisition of mathematical skills or carbohydrate estimation skills.

REVIEWER	Paul McArdle Birmingham Community Healthcare NHS Foundation Trust, UK.
REVIEW RETURNED	16-Apr-2019

GENERAL COMMENTS	This is an interesting and well-designed study. It's outcomes will be of interest to those delivering diabetes education across the globe, however I did initially wonder if there was a need for such a study. 'ACC' (although not called that in my clinical practice) is seen as the 'Gold Standard' and should be offered to all people with Type 1 Diabetes who are prepared to do the number of injections etc. in the form of the DAFNE programme, for example. However, the applicability in the UK may be for those patients who don't / can't do something like DAFNE and we don't currently have anyhting clearly defined for the next level down. This seems to be where this study will make a contribution to the evidence base and

	so I do think it is of value. I have noted a few comments below which I hope you will find helpful. Limitation: the lack of a dietary control group - it's worth stating that this would probably be considered unethical! Introduction: The terms BCC and ACC are not commonly-used in clinical practice the UK, nor possibly other countries. Whilst they are well-described in the manuscript it may be worthwhile referring to other commonly-used terms. For example in the UK the term 'Carbohydrate Awareness' is often used to describe basic carbohydrate counting (where there is no precise counting and insulin dose adjustment)... although typically in T2DM. A reference / citation is needed to substantiate the claim that 'systematic educating and training is still not offered routinely for patients on MDI therap in outpatient clinics in Denmark'. Page 5, line 54: this sentance should stat with 'In...'? Methods: p7 line 32: there is a relatively well-accepted definition of Low Carbohydrate (50-130g carbohydrate per day) which you may like to refer to. See Feinman et al 2015. p8. There is a key difference between BCC and ACC besides the use of the ABC etc, which is that BCC is 2 x 3h groups, plus 1 x 2h groups, whereas ACC is 1 x 4h group plus 2 x 45 minutes individual sessions. This inconsistency in the mode of delivery / level of input per patient of the two interventions requires further justification so that it is not perceived as a bias or limitation of the study design. Or if it is such... acknowledge it as so. How is the risk of contamination going to be reduced? Will the professionals delivering the interventions work acoss the intervention / control. Will they be held in different clinics to avoid patient contamination etc? p10, line 43: this should read "is" rather than "in' Other points... Exclusion criteria: Why exclude those on fixed doses of rapid acting meal time insulin...? Surely these are the types of patients who may want to or benefit from BCC or ACC? Will the analysis of the weighed food records be blinded? The manuscript should include a clearer statement of the funding of the study, including whether Roche funded the ABC.

REVIEWER	Sian Rilstone Imperial College Healthcare NHS Trust
REVIEW RETURNED	21-Apr-2019

GENERAL COMMENTS	An interesting study, that will assess whether there are other options for optimising diabetes self management other than advanced carbohydrate counting which, in the UK would be DAFNE which is considered the gold standard. Considering other options, particularly for those with poor literacy skills is important. With regard to the question "Are the methods described sufficiently to allow the study to be repeated?" - the methodology is clearly described, however without knowing the content and learning outcomes of the education it would be impossible to repeat

	replicate the study. The authors may want to consider making their curriculum and educational resources available, maybe at a later date. I note that the BCC intervention is three sessions totalling 8 hours, whereas the ACC is tow sessions totalling 5.5 hours. This difference in HCP input and therefore support may influence the participants learning, and therefore could be considered a weakness in the study design. It seems a shame that CGM isn't repeated at week 48.

REVIEWER	Wilson Tam National University of Singapore, Singapore
REVIEW RETURNED	14-May-2019

GENERAL COMMENTS	Review of methodology and statistical analysis I think the described methodologies in the protocol are fine in general, just the authors may need to clarify some points that I listed below. The section of statistical analysis may need to modify as it doesn't look quite good. Randomization subsection It was mentioned that the randomization is done by stratifying participants based on sex and HbA1c at baseline. Could the authors specify what is the cut-off value(s) for HbA1c? Please also specify the block size. Intervention and control groups subsection The control group will receive the usual care but whether the ABC-ACC and BCC group will receive the described interventions on top of the usual care? Please clarify From Figure 2, I understand the timeline of the group education sessions (at week 0 & 2 for BBC and 0 for ABC-ACC) but it may be better to describe in the text. Also, week 0 or week 1? Usually week 0 is referred before the start of the intervention (but I leave it to the authors) Data collection subsection Table 1 showed the schedule of measuring the outcome, I suppose MAGE would also be measured as the same time as HbA1c? How many items for the DDRQol? Whether the 5-item short form of HCCQ was validated? Mathematical literacy questionnaire was validated in your population or not? Would it be possible to include the full questionnaire in the supplementary file? Data analysis plan subsection It was mentioned "detect a clinically meaningful difference in change in HbA1c of 3.5 mmol/mol between the BCC group versus the control group" Any reference to support 3.5 is a clinical meaningful difference? For the computation of sample size for MAGE, it was mentioned "to detect a clinically meaningful difference in the change in MAGE during the intervention period (week 24) of ≥0.35 mmol/l (SD 0.7 mmol/l) between the study groups" Authors mentioned a previous study reported a change of 4.8 but then they used difference of

	0.35 and sd 0.7. Also, given these 2 values, I think the sample size is still 64 not 77? (as the effect size is still 0.35/0.7 =0.5) Also, no attrition rate was taken into consideration for the sample size estimation. Statistical methods subsection For descriptive statistics, author mentioned that they would use Mean (SD) and Median (IQR) for normal and non-normal variables, it is fine. Then I think the authors may need to describe the compare the baseline data between the 3 groups, they can use one-way ANOVA for normal data or Kruskal-Wallis H test for non-normal data. For within group comparison, they can consider to use Paired samples t-test for normal data or Wilcoxon Sign-rank test for non-normal data. For comparing the change and between group, they can consider to use Repeated Measured ANOVA, Generalized Estimating Equation (GEE) or Linear Mixed Models. Please note that "Plots of residuals versus predicted values will be used to judge normality" is mainly used for judging the homoscedasticity of the residuals in regression. To judge the normality of a variable, we can examine the QQ plot or use the Shapiro-Wilk or Kolmogorov-Smirnov test. I think the authors can consult a statistician to modify the statistical methods part as it doesn't seem in a logical order. Some minor comments I think the authors can consider to combine Figure 1 and 2 as the latter provide more information.

REVIEWER	LM Ho School of Public Health The University of Hong Kong
REVIEW RETURNED	28-May-2019

GENERAL COMMENTS	My review is focused on statistical methods and analyses proposed. 1) The study will adopt stratified randomization based on sex and HbA1c at baseline. These stratified variables should be additionally adjusted in all statistical analyses, or otherwise the treatment effects will be biased (Kahan and Morris 2011). 2) The use of mixed effects models is more appropriate than general linear models as some measurements, eg HbA1c and blood pressure, will be repeatedly measured at several times. 3) To handle missing values, the last observation carried forward approach, although simpler, will underestimate the variability of the measurements, and will result in inflation of Type I error rate. A better approach will be to use multiple imputation.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1	**Answer/rebuttal**

Reviewer Name: Nicole Farmer Institution and Country: National Institutes of Health Clinical Center	
The authors state that a limitation is lack of a dietary untreated control group. I would agree but present that having this control group may go against standard of care for type 1 diabetics, and thus having it as a randomized group may insert ethical issues.	Correct. It would be unethical to have an untreated control group We have inserted the reviewer's point under the "Strengths and Limitations of the study" section.
I think there is another limitation present which the authors may consider when reviewing their results. The BCC group has group modelling and more group time than the ACC or the control group. Group effects of modelling, experiential learning from others may play a part in any intervention effect, as much as acquisition of mathematical skills or carbohydrate estimation skills.	We thank the reviewer for her relevant comments. We will consider and discuss this suggestion in relation to our study results.
Reviewer: 2 Reviewer Name: Paul McArdle Institution and Country: Birmingham Community Healthcare NHS Foundation Trust, UK.	**Answer/rebuttal**
- Limitation: the lack of a dietary control group - it's worth stating that this would probably be considered unethical!	Exactly. It would be unethical. We have inserted the reviewer's point under the "Strengths and Limitations of the study" section.
Introduction: The terms BCC and ACC are not commonly-used in clinical practice the UK, nor possibly other countries. Whilst they are well-described in the manuscript it may be worthwhile referring to other commonly-used terms. For example, in the UK the term 'Carbohydrate Awareness' is often used to describe basic carbohydrate counting (where there is no precise counting and insulin dose adjustment) although typically in T2DM.	We acknowledge the reviewer's suggestion using the term "carbohydrate awareness" but we think the term "basic carbohydrate counting" describes and defines this educational level very well. Additionally, both the Canadian and American diabetes guidelines use the term basic and advanced levels of carbohydrate counting. The reference used in our manuscript for defining the levels is: Gillespie SJ, Kulkarni KD, Daly AE. Using carbohydrate counting in diabetes clinical practice. J Am Diet Assoc. 1998;98(8):897-905.

Introduction: A reference / citation is needed to substantiate the claim that 'systematic educating and training is still not offered routinely for patients on MDI therapy in outpatient clinics in Denmark'.	Unfortunately, no references are available as no studies have been conducted examining this in Denmark. However, the author corresponding author Bettina Ewers has been Head of Nutrition at Steno Diabetes Center Copenhagen for the last 10 years and has a large network of Danish dietitians working in the field of dietary treatment of patients with type 1 diabetes why she would know if any such studies had been carried out or planned.
Introduction: Page 5, line 54: this sentence should state with 'In...'?	Unfortunately, we were not able to find this error in the original manuscript which you reviewed.
Methods: p7 line 32: there is a relatively well-accepted definition of Low Carbohydrate (50-130g carbohydrate per day) which you may like to refer to. See Feinman et al 2015.	We thank the reviewer for the proposal. However, in Feinman et al 2015 it is pointed out that there is a lack of agreement on definitions of low-carbohydrate diets. The recently published ADA report (Nutrition Therapy for Adults with Diabetes or Prediabetes: A Consensus Report. Diabetes Care 2019) similarly states…"There is no consistent definition of "low" carbohydrate. In this review, a low-carbohydrate eating pattern is defined as reducing carbohydrates to 26–45% of total calories". This definition is close to our exclusion criteria of a low carbohydrate intake below 25 E%.
p8. There is a key difference between BCC and ACC besides the use of the ABC etc, which is that BCC is 2 x 3h groups, plus 1 x 2h groups, whereas ACC is 1 x 4h group plus 2 x 45 minutes individual sessions. This inconsistency in the mode of delivery / level of input per patient of the two interventions requires further justification so that it is not perceived as a bias or limitation of the study design. Or if it is such... acknowledge it as so.	We thank the reviewer for pointing this out. The BCC and ACC including the ABC concepts were originally developed and tested separately and are in our study compared with standard dietary treatment. We are aware of the possible limitations of the difference in the number of hours and type of educational support that each of the three groups are being provided. We have tried to make the groups comparable, since the number of visits with a dietitian is the same in all three groups. We will however, consider and discuss the possible limitations of these differences when interpreting and publishing the study results.
How is the risk of contamination going to be reduced? Will the professionals delivering the interventions work across the intervention/control. Will they be held in	It will be the same study dietitians delivering the educational program in both the standard treatment group and the intervention groups. The dietitians have been trained by the PI (Bettina Ewers) in what to deliver in each study-arm

different clinics to avoid patient contamination etc?	according to the study protocol and in case of doubt, they will discuss each case with the PI to make sure that they provide the correct guidance to all participants. Data on which of the dietitians each participant has been exposed to during the trial is registered for later data analysis. Additionally, all study dietitians have an interest in providing the best possible dietary guidance irrespective of it being the standard treatment or the two intervention concepts being tested.
p10, line 43: this should read "is" rather than "in'	Unfortunately, we were not able to find this error in the original manuscript which you reviewed.
Exclusion criteria: Why exclude those on fixed doses of rapid acting meal time insulin...? Surely these are the types of patients who may want to or benefit from BCC or ACC?	Thank you for the comment. We agree and have only excluded patients on use split-mixed insulin therapy in the study. The sentence will be deleted from the manuscript.
Will the analysis of the weighed food records be blinded?	The dietitian performing the analysis of the food records only have access to the study ID number and participant initials.
The manuscript should include a clearer statement of the funding of the study, including whether Roche funded the ABC.	On page 14 in our manuscript we have a clear funding statement. We have added the following sentence to the statement: “Roche has provided voucher codes for free use of the bolus calculator “MySugr Pro” in the 12-month trial period for patients randomized to the ACC group in the study”.
Reviewer: 3 Reviewer Name: Sian Rilstone Institution and Country: Imperial College Healthcare NHS Trust	**Answer/rebuttal**
With regard to the question "Are the methods described sufficiently to allow the study to be repeated?" - the methodology is clearly described, however without knowing the content and learning outcomes of the education it would be impossible to repeat replicate the study. The authors may want to consider making their curriculum and educational resources available, maybe at a later date.	We thank the reviewer for this very important point. The curriculums will be made available once the study results have been published.
I note that the BCC intervention is three sessions totalling 8 hours, whereas the ACC is two sessions totalling 5.5 hours. This	We thank the reviewer for pointing this out.

difference in HCP input and therefore support may influence the participants learning, and therefore could be considered a weakness in the study design.	We are aware of the possible limitations of the difference in the number of hours of education and support in each of the intervention groups. We are testing two concepts (BCC and ACC-ABC) which have been developed and tested in different settings previously and provided positive results. We will consider and discuss the possible limitations of these differences when interpreting and publishing the study results.
It seems a shame that CGM isn't repeated at week 48.	We agree, however reducing the trial burden for the patients was more important since the primary outcome is change in CGM-data after 6-months intervention and not 12-months.
Reviewer: 4 Reviewer Name: Wilson Tam Institution and Country: National University of Singapore, Singapore	**Answer/rebuttal**
Randomization subsection It was mentioned that the randomization is done by stratifying participants based on sex and HbA1c at baseline. Could the authors specify what is the cut-off value(s) for HbA1c? Please also specify the block size.	The cut-off value for HbA1c was < 61 or ≥ 61 mmol/mol based on median HbA1c of patients with type 1 diabetes in our clinic within the last year. The block size is 6 (based on 3 groups, sex and HbA1c).
Intervention and control groups subsection The control group will receive the usual care but whether the ABC-ACC and BCC group will receive the described interventions on top of the usual care? Please clarify.	In the Methods' section we have described what will be delivered in each group. The ABC-ACC and BCC group will not receive usual care.
From Figure 2, I understand the timeline of the group education sessions (at week 0 & 2 for BBC and 0 for ABC-ACC) but it may be better to describe in the text. Also, week 0 or week 1? Usually week 0 is referred before the start of the intervention (but I leave it to the authors).	We would prefer to leave it this way.
Data collection subsection Table 1 showed the schedule of measuring the outcome, I suppose MAGE would also be measured as the same time as HbA1c?	MAGE is measured in the six following days after measuring HbA1c. It has been added to Table 1 that MAGE (CGM), dietary registration and urine collection are being measured/collected after the study visits.
Data collection subsection 1) How many items for the DDRQol? 2) Whether the 5-item short form of HCCQ was validated? 3) Mathematical literacy questionnaire was	1) The DDRQOL 31-item scale. This has been added to the manuscript. 2) Yes, the HCCQ has been validated. This has been added in the manuscript.

validated in your population or not? 4) Would it be possible to include the full questionnaire in the supplementary file?	3) The mathematical literacy questionnaire has not been validated but is based on a validated questionnaire from the US. Our questionnaire has been feasibility tested for use in our population according to understanding the questions and level of difficulties of questions. 4) No, the questions are in Danish and will be not be translated and published in a supplementary file until the study results are being published.
Data analysis plan subsection It was mentioned “detect a clinically meaningful difference in change in HbA1c of 3.5 mmol/mol between the BCC group versus the control group” Any reference to support 3.5 is a clinical meaningful difference?	In the Diabetes Control and Complications Trial (DCCT) achieving a difference of HbA1c lowering of at least 0.5% reduced the risk of microvascular complications in the intensively-treated group (using basal-bolus or pump therapy) Ref.: Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993;329(14):977-986.
Data analysis plan subsection For the computation of sample size for MAGE, it was mentioned “to detect a clinically meaningful difference in the change in MAGE during the intervention period (week 24) of ≥0.35 mmol/l (SD 0.7 mmol/l) between the study groups” Authors mentioned a previous study reported a change of 4.8 but then they used difference of 0.35 and sd 0.7. Also, given these 2 values, I think the sample size is still 64 not 77? (as the effect size is still 0.35/0.7 =0.5) Also, no attrition rate was taken into consideration for the sample size estimation.	The sample size if 77 is including an expected drop-out rate of 20% to maintain sufficient power in the study. Thus, the number 64 is without the attrition rate.
Statistical methods subsection For descriptive statistics, author mentioned that they would use Mean (SD) and Median (IQR) for normal and non-normal variables, it is fine. Then I think the authors may need to describe the compare the baseline data between the 3 groups, they can use one-way ANOVA for normal data or Kruskal-Wallis H test for non-normal data. For within group comparison, they can consider to use Paired samples t-test for normal data or Wilcoxon Sign-rank test for non-normal data. For	We thank the reviewer for his comments and suggestions. We have inserted the suggestions in the Statistical Methods section.

comparing the change and between group, they can consider to use Repeated Measured ANOVA, Generalized Estimating Equation (GEE) or Linear Mixed Models.	
Please note that "Plots of residuals versus predicted values will be used to judge normality" is mainly used for judging the homoscedasticity of the residuals in regression. To judge the normality of a variable, we can examine the QQ plot or use the Shapiro-Wilk or Kolmogorov-Smirnov test.	We agree. Examinations of the relevant diagnostic plots, including QQ-plots, will be used to evaluate normality of the residuals.
I think the authors can consult a statistician to modify the statistical methods part as it doesn't seem in a logical order.	We acknowledge the statistical challenges in such a study. Therefore, we did consult a statistician when we wrote this section.
I think the authors can consider to combine Figure 1 and 2 as the latter provide more information.	We prefer separate figures since Figure 1 is a study overview/timeline and Figure 2 provides a detailed description of the study visits in each arm.
Reviewer: 5 Reviewer Name: LM Ho Institution and Country: School of Public Health, The University of Hong Kong	**Answer/rebuttal**
1) The study will adopt stratified randomization based on sex and HbA1c at baseline. These stratified variables should be additionally adjusted in all statistical analyses, or otherwise the treatment effects will be biased (Kahan and Morris 2011).	Yes, we will adjust for the stratified variables in all statistical analyses.
2) The use of mixed effects models is more appropriate than general linear models as some measurements, e.g. HbA1c and blood pressure, will be repeatedly measured at several times.	We agree, and we will use mixed effects models in our data analysis. This has been added to the Statistical Methods section.
3) To handle missing values, the last observation carried forward approach, although simpler, will underestimate the variability of the measurements, and will result in inflation of Type I error rate. A better approach will be to use multiple imputation.	We thank the reviewer for the comment. We will use the last observation carried forward approach and use the multiple imputation approach in a sensitivity analysis.

VERSION 2 – REVIEW

REVIEWER	LM Ho School of Public Health, The University of Hong Kong
REVIEW RETURNED	04-Jul-2019

GENERAL COMMENTS	This version has been improved. I have no other comments.

VERSION 2 – AUTHOR RESPONSE

I have proofread my manuscript carefully and corrected all errors. Additionally, I have added the requested information (two sentences) to my manuscript.