PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Effectiveness of Real-Time Continuous Glucose Monitoring to Improve Glycaemic Control and Pregnancy Outcome in Patients with Gestational Diabetes Mellitus: A Study Protocol for a Randomised Controlled Trial.
AUTHORS	Huhn, Evelyn; Linder, Tina; Eppel, Daniel; Weißhaupt, Karen; Klapp, Christine; Schellong, Karen; Henrich, Wolfgang; Yerlikaya-Schatten, Gülen; Rosicky, Ingo; Husslein, Peter; Chalubinski, Kinga; Mittlbock, Martina; Rust, Petra; Hoesli, Irene; Winzeler, Bettina; Jendle, Johan; Fehm, T; Icks, Andrea; Vomhof, Markus; Greiner, Gregory; Szendrödi, Julia; Roden, Michael; Tura, Andrea; Göbl, Christian

VERSION 1 – REVIEW

REVIEWER	Evgenii Pustozerov Saint Petersburg State Electrotechnical University, Russia Almazov National Medical Research Centre, Russia
REVIEW RETURNED	29-Jun-2020

GENERAL COMMENTS	The research topic is urgent. There is a big demand in controlled trials evaluating effect of CGM in GDM patients. The study conducted in accordance with the presented protocol will contribute a lot to the body of knowledge. The protocol is written in clear scientific language. Intervention strategy, primary and secondary goals, data analysis and sample size evaluation are carried out accurately and described plainly. An essential cost-effectiveness analysis is also included in the study. The references provided in the protocol applicable and sufficient. Minor comments: Page 6, line 36. LGA acronym should be spelled out in the abstract. Page 15, line 13. For readers without experience with Dexcom CGM systems, a clarification of why there won't be calibration might be helpful. Page 15, line 48. A more common term is "desktop".

REVIEWER	David Rodbard Biomedical Informatics Consultants LLC USA
REVIEW RETURNED	02-Jul-2020

GENERAL COMMENTS	1. The IGC has the advantage that the limits for ht target range can be customized, and in particular customized to the limits the authors believe are most appropriate for pregnancy. In addition to the IGC, the authors should consider using LBGI (LGI) and HBGI

	(HGI). A recent paper by N. Oliver and Moscada discusses ways to select the best limits for target range in order to achieve the best Coefficient of Determination (greatest ability to distinguish between individuals, over and above the measurement error and random error within individuals)

REVIEWER	Denice Feig University of Toronto Canada I have been a Speaker and on an Advisory Board for Medtronic in 2018.
REVIEW RETURNED	08-Jul-2020

GENERAL COMMENTS	This is a well written and important RCT protocol for the study of rt-CGM in women with gestational diabetes. I have some comments and suggestions. Abstract: 1. Please state clearly the objective of the study, and the primary outcome of the study. 2. Please state the gestational weeks of inclusion to the study. 3. This is an awkward sentence starting with “From second to third visit…” I suggest you modify it to “The control group will receive a blinded CGM from the second to third visit as well as between gestational week 36+0 and 38+6 for 10 days” or something like that. Introduction 4. It is not clear from the stated ‘aim of this proposal’ what the primary research question is and what the primary outcome is. The sample size has been done to show a reduction in %LGA, so one would think this is your primary outcome, but it is not evident in the proposal. 5. One aim is to show undetected hyper or hyperglycemia using SMBG vs rt-CGM. This has been done in the past by Yogev et al Obstet Gynecol 2003;101:633– 8, so it is suggested that this be included in the introduction. 6. The introduction should include the authors’ hypothesis regarding the primary outcome. Methods and analysis 7. Under Exclusion criteria, it says that in order to diagnose overt diabetes during pregnancy, the results will need to be confirmed by repeated testing. Do the researchers feel this needs to be done during pregnancy? I don’t think this is what the ADA intended. This refers to making the diagnosis outside of pregnancy. Please clarify. 8. Page 9, the authors refer to a run-in period. What occurs in the run-in period? 9. I was surprised to see that either insulin or metformin can be used as the intervention, as metformin will muddy the primary outcome of LGA. How do the authors plan to handle this in the analysis? 10. Is the analysis for the primary outcome ‘intention-to-treat’? 11. What will happen if the unblinded investigator downloads the blinded CGM data but there is no data or very little? Is there a possibility to redo? Is there a minimum amount of data that is required? 12. I would suggest that a diagram of the time-line of the visits be done. I believe it is referred to in the text but I could not see it.

	13. Which growth chart will be used when assessing for LGA and SGA? 14. The health economic evaluation will be dependent on the # of LGA cases avoided. What if the # avoided is 0 or even increased? Will this still be done? 15. Is there a stopping plan for either safety or feasibility? 16. Is there a DSMB committee to oversee the trial? 17. Is there a data monitoring committee? 18. The Dexcom company will be funding this trial. I didn't see any statement regarding the funder's involvement in study design, collection of data, management of trial, analysis of data, interpretation of data, writing of the report or decision to submit for publication. 19. What will the investigators do if there are cross-overs ie subjects in the control group use Dexcom G6 or Freestyle libre? 20. Are the investigators monitoring compliance ie time CGM is worn?

VERSION 1 – AUTHOR RESPONSE

RESPONSE TO REVIEWER 1:
Our team appreciates the encouragements and constructive comments of the reviewer as well as the efforts regarding the improvement of the manuscript.

Comment: Page 6, line 36. LGA acronym should be spelled out in the abstract.
Response: Thank you for pointing out this inaccuracy, the acronym is now spelled out. (page 3, line 10)

Comment: Page 15, line 13. For readers without experience with Dexcom CGM systems, a clarification of why there won't be calibration might be helpful.
Response: The Dexcom G6 system is calibration-free. As the original sentence was leading to misinterpretation, we have revised it for more clarity. (page 12, line 14)

Comment: Page 15, line 48. A more common term is "desktop".
Response: We agree and changed the term within the revised manuscript. (page 12, line 37)

RESPONSE TO REVIEWER 2:
Our team appreciates the constructive comment of the reviewer which improves our manuscript greatly.

Comment: The IGC has the advantage that the limits for ht target range can be customized, and in particular customized to the limits the authors believe are most appropriate for pregnancy. In addition to the IGC, the authors should consider using LBGI (LGI) and HBGI (HGI). A recent paper by N. Oliver and Moscada discusses ways to select the best limits for target range in order to achieve the best Coefficient of Determination (greatest ability to distinguish between individuals, over and above the measurement error and random error within individuals).
Response: We agree that LBGI and HBGI would add valuable insights to determine the glycaemic control patients might be able to achieve by using rt-CGM. We have therefore added those indices to our manuscript and thank the reviewer for this important input. (page 13, line 15, new reference 25)

RESPONSE TO REVIEWER 3:

We highly appreciate the effort you have put into the revision of our manuscript and thank you for the positive and supportive feedback which is very helpful to improve the quality and readability of our manuscript.

Comment: Please state clearly the objective of the study, and the primary outcome of the study.
Response: We agree that the rationale of the study is not well reflected in the abstract. We have reedited the abstract accordingly. (page 3, line 9 ff)

Comment: Please state the gestational weeks of inclusion to the study.
Response: The gestational weeks of inclusion are already stated within the “inclusion criteria” section; however, as this paragraph is not very clear on this point, we have rephrased it and put the gestational weeks also within the materials and methods section of the abstract. (page 3, line 19)

Comment: This is an awkward sentence starting with "From second to third visit..." I suggest you modify it to "The control group will receive a blinded CGM from the second to third visit as well as between gestational week 36+0 and 38+6 for 10 days" or something like that.
Response: Thank you very much for your help in improving the readability of this manuscript. We rephrased the sentence. (page 3, line 24)

Comment: It is not clear from the stated 'aim of this proposal' what the primary research question is and what the primary outcome is. The sample size has been done to show a reduction in %LGA, so one would think this is your primary outcome, but it is not evident in the proposal.
Response: The difference in %LGA newborns between the intervention and control group is indeed our primary outcome. There is a “primary and secondary outcome” section within the introduction. However, we have placed the primary outcome within the abstract and also the hypotheses section for more clarity. (page 3, line 11; page 6, line 22)

Comment: One aim is to show undetected hyper or hyperglycemia using SMBG vs rt-CGM. This has been done in the past by Yogev et al Obstet Gynecol 2003;101:633– 8, so it is suggested that this be included in the introduction.
Response: Thank you for pointing this important study out, which focuses on type 1 diabetes mellitus patients in pregnancy. We included it into the introduction section. (page 5, line 14ff, new reference number 10)

Comment: The introduction should include the authors' hypothesis regarding the primary outcome.
Response: We rephrased the “hypotheses” section of our introduction accordingly. (page 6, line 22)

Comment: Under Exclusion criteria, it says that in order to diagnose overt diabetes during pregnancy, the results will need to be confirmed by repeated testing. Do the researchers feel this needs to be done during pregnancy? I don't think this is what the ADA intended. This refers to making the diagnosis outside of pregnancy. Please clarify.
Response: Thank you for hinting to this mistake. The original manuscript erroneously stated that retesting is necessary in the case of unequivocal hyperglycemia; of course retesting is only recommended in the absence of unequivocal hyperglycemia. We rephrased the sentence. The sentence refers to women with pathological blood glucose values before week 24 of gestation who do not meet the criteria for the diagnosis of type 1 or 2 diabetes. Those women will receive a 2h-75g-OGTT between weeks 24+0 and 28+6 for further diagnosis as current clinical practice guidelines recommend. The diagnosis of GDM before week 24 of gestation is controversial.[1] (page 8, line 22)
Comment: Page 9, the authors refer to a run-in period. What occurs in the run-in period?
Response: At the first visit, all patients are advised on self-monitoring of their blood glucose levels (SMBG) by using a standard blood glucose meter and logbook and also receive dietary recommendations according to the standards of care. During the run in period, patients will get used

to the glucose monitoring and tracking and will be able to get all corresponding questions answered before randomization. (page 9, line 5)

Comment: I was surprised to see that either insulin or metformin can be used as the intervention, as metformin will muddy the primary outcome of LGA. How do the authors plan to handle this in the analysis?
Response: Our hypothesis is that the use of rt-CGM and subsequent dietary, behavioral and pharmacological adaptations lead to a reduced incidence of LGA newborns as compared to self-monitoring by fingerstick. At each site, patients will be treated according to the country's clinical practice guidelines. In Sweden, for example, Metformin is a first line treatment for GDM. The primary question is if the sum of all interventions based on the additional information of rt-CGM leads to a reduced number of LGA newborns; not if Metformin or Insulin are more efficient to reduce the LGA incidence. However, all interventions will be tracked and documented and post-hoc analyses will provide further insights into the underlying mechanisms. (manuscript has not been changed)

Comment: Is the analysis for the primary outcome 'intention-to-treat'?
Response: Yes, this is stated in the section "analysis plan". (page 18, line 4)

Comment: What will happen if the unblinded investigator downloads the blinded CGM data but there is no data or very little? Is there a possibility to redo? Is there a minimum amount of data that is required?
Response: If the Dexcom receiver does not receive signals from the sensor or if there are errors (for example not enough data points per time slot) the patient will receive an alarm. Patients will be advised to contact the study team in case of an alarm so that the system can be checked or replaced. We have inserted a corresponding sentence into the manuscript. (page 11, line 12)

Comment: I would suggest that a diagram of the time-line of the visits be done. I believe it is referred to in the text but I could not see it.
Response: A flow chart is certainly helpful for a better understanding of the patient flow; we have therefore included one into the manuscript. (uploaded as separate image file)

Comment: Which growth chart will be used when assessing for LGA and SGA?
Response: The growth charts are stated within the manuscript, see reference 44. (page 15, line 29)

Comment: The health economic evaluation will be dependent on the # of LGA cases avoided. What if the # avoided is 0 or even increased? Will this still be done?
Response: The health economic evaluation aims at analyzing efficiency of the intervention. Even if there are no LGA cases avoided or the number of LGA cases is increased in the intervention group, the intervention might be efficient if costs in the intervention group are sufficient low in comparison to the control group. Thus, we will perform a health economic evaluation regardless of the main result to inform about efficiency of the intervention. Thank you for mentioning this important point, we have included a corresponding statement within the manuscript. (page 17, line 2)

Comment: Is there a stopping plan for either safety or feasibility?
Response: There is no designated stopping plan. The study is supervised by a DSMB committee and the Austrian Agency for Health and Food Safety. In case the study has to be stopped (for example due to serious adverse events), all patients will be treated according to the standards of care at the institution where they were recruited. (manuscript has not been changed)

Comment: Is there a DSMB committee to oversee the trial?
Response: The trial will be overseen by the KKS (http://www.kks-netzwerk.at/, Competence Center for Clinical Trials) in Austria; similar independent committees will oversee the trials at the other sites in

Switzerland, Germany and Sweden. We have included a statement within the manuscript. (page 17, line 25)

Comment: Is there a data monitoring committee?
Response: The DSMB committee will also monitor the data quality and accuracy. (page 17, line 25)

Comment: The Dexcom company will be funding this trial. I didn't see any statement regarding the funder's involvement in study design, collection of data, management of trial, analysis of data, interpretation of data, writing of the report or decision to submit for publication.
Response: Thank you for indicating this inaccuracy. Dexcom was and is not involved in study design, collection, analysis and interpretation of data, management of the trial, writing of the report or decision to publish. We have extended the corresponding paragraph accordingly. (page 19, line 14)

Comment: What will the investigators do if there are cross-overs ie subjects in the control group use Dexcom G6 or Freestyle libre?
Response: As patients are first diagnosed with GDM by the participating site and then enrolled into the study, it is the site's responsibility to correctly randomize them and equip them accordingly (standard blood glucose meter for SMBG and/or the Dexcom G6 for rt-CGM). The patients will be advised not to use other systems than the ones provided to them by the recruiting site. Should a patient decide to seek external consulting or treatment and to use other systems than the ones provided to them, the patient's reasons will have to be evaluated and an exclusion from the study, in agreement with the patient's wishes, might be necessary. (manuscript has not been changed)

Comment: Are the investigators monitoring compliance ie time CGM is worn?
Response: Dexcom's Clarity software which is used by the study team to monitor the data of all patients contains metrics to check for compliance. It is, for example, not possible to extract the sensor and put it back on later. We put a corresponding statement within the manuscript. (page 11, line 27).

REFERENCES:

1. McIntyre HD, Sacks DA, Barbour LA, Feig DS, Catalano PM, Damm P, McElduff A. Issues With the Diagnosis and Classification of Hyperglycemia in Early Pregnancy. Diabetes Care. 2016 Jan 1;39(1):53–4.

VERSION 2 – REVIEW

REVIEWER	Prof Denice Feig Mount Sinai Hospital and University of Toronto Canada
REVIEW RETURNED	18-Aug-2020

GENERAL COMMENTS	The changes made are acceptable.