PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Protocol for a feasibility randomized control trial for continuous glucose monitoring in type 1 diabetes patients at rural, first-level hospitals in rural Malawi
AUTHORS	Adler, Alma; Ruderman, Todd; Valeta, Francis; Drown, Laura; Trujillo, Celina; Ferrari, Gina; Msekandiana, Amos; Wroe, Emily; Kachimanga, Chiyembekezo; Bukhman, Gene; Park, Paul

VERSION 1 – REVIEW

REVIEWER	Dickson, Lynnsay University of the Witwatersrand, Paediatrics
REVIEW RETURNED	11-Jul-2021

GENERAL COMMENTS	Thank you for this important initiative, which may improve clinical outcomes for type 1 diabetes patients living in LIC. In the pre-trial training, will participants in both groups be encouraged to self-titrate insulin doses, based on their self-monitored blood glucose results? (Page 8, Line 29-30)

REVIEWER	Black, Sheila University of Alabama, Psychology13-Jul-2021
REVIEW RETURNED	13-Jul-2021

GENERAL COMMENTS	This study addresses a very important issue: the feasibility or effectiveness of CGM in low-income countries in which the residents have limited access to important resources (e.g., electricity). The study was well-designed and should make an important contribution to the literature. I would like for the authors to include more information about the inclusion criteria. A number of children have Type 1 diabetes. Will they be allowed to enter the study? If so, how will they deal with obtaining assent from the children and consent from their parents. With regard to adults, will they make sure that the adults are free of intellectual disabilities and/or dementia? In addition, will they only recruit literate adults or will literacy not be an issue? My other concern involved the criteria that will be used to indicate that the intervention is feasible. Will participants have to complete a certain percentage of the outcome measures (e.g., logging glucose readings, number of times home glucose meters used to test blood sugar). Do the authors predict that both the control and the experimental group will be comparable in their willingness to adhere to the study protocol?

	Overall, I really like this study and believe that it addresses an important issue.

REVIEWER	Moran, Antoinette University of Minnesota System
REVIEW RETURNED	14-Nov-2021

GENERAL COMMENTS	Overall this is a worthy project in the effort to advance T1D control in Africa and other low resource countries. I just have a few minor comments: 1. Will insulin insecurity be a problem? They say nothing about how patients receive insulin. 2. I'm a little dubious of their sample size calculations given that they will include all subjects including new onset, who may have significant HbA1c drops as they enter the honeymoon. Nonetheless this this is a feasibility study so efficacy power is not so important. 3. How to they expect COVID-19 to impact study procedures and do they have a contingency plan? 4. What about CGM time-in-range as an outcome? There are many factors that can cause spurious HbA1c results in Africa---sickle cell disease/trait, iron deficiency, chronic malaria, etc.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Lynnsay Dickson, University of the Witwatersrand Comments to the Author:
Thank you for this important initiative, which may improve clinical outcomes for type 1 diabetes patients living in LIC.
In the pre-trial training, will participants in both groups be encouraged to self-titrate insulin doses, based on their self-monitored blood glucose results? (Page 8, Line 29-30)

Current clinical practice at these sites does not encourage patients to self-titrate insulin doses, due to risk of severe hypoglycemia if doses are titrated incorrectly. In line with current practice we will not be encouraging patients to self-titrate. We are instead focusing on encouraging providers to help patients problem-solve possible scenarios around diabetes management that may require adjusting insulin doses (e.g., food insecurity and illness). CGM use in this setting, especially knowing which direction blood glucose levels are trending, can be an effective tool for teaching patients how to make decisions regarding treatment (give lower dose of insulin, wait until BGs are back in range before taking insulin, amount of carbs eaten, treating hypoglycemia before if happens if they see BG is dropping fast) and creating a pathway for patients to reach out to health care workers.

We have added the sentence: In line with current practice we will not be encouraging patients to self-titrate. We are instead focusing on encouraging providers to help patients problem-solve possible scenarios around diabetes management that may require adjusting insulin doses (e.g., food insecurity and illness)

Reviewer: 2
Dr. Sheila Black, University of Alabama Comments to the Author:

This study addresses a very important issue: the feasibility or effectiveness of CGM in low-income countries in which the residents have limited access to important resources (e.g., electricity). The study was well-designed and should make an important contribution to the literature.

I would like for the authors to include more information about the inclusion criteria. A number of children have Type 1 diabetes. Will they be allowed to enter the study? If so, how will they deal with obtaining assent from the children and consent from their parents. With regard to adults, will they make sure that the adults are free of intellectual disabilities and/or dementia?
In addition, will they only recruit literate adults or will literacy not be an issue?

We have attached copies of the assent and consent forms, both that have been approved by the Mass General Brigham and Malawi IRB. Our approval includes conducting this study in children, and the youngest patient at the clinics is 8 years old.

A high proportion of patients in rural Malawi are not literate, so that is one of the main reasons that we are conducting this as a feasibility study, and we are not excluding patients based on literacy. No patients with intellectual disabilities or dementia will be included.

We have added some information on page 6.

“All participants will be required to sign an informed consent form on the day of enrollment (Appendix A). Assent will be collected from children under the age of 18 (Appendix B). Patients will be enrolled regardless of literacy. No patients with mental impairment will be included. “

My other concern involved the criteria that will be used to indicate that the intervention is feasible. Will participants have to complete a certain percentage of the outcome measures (e.g., logging glucose readings, number of times home glucose meters used to test blood sugar). Do the authors predict that both the control and the experimental group will be comparable in their willingness to adhere to the study protocol?

In our previous experience with these patients, they are very willing to participate in activities to increase their knowledge and ability to control their T1D. Most of the patients already are able to use their home glucometers. We are looking to test if they are equally able to adhere to CGM Technology. We do not intend to have cutoffs for outcome measures as there are no established guidelines. Additionally if patients don’t do the manual logging but wear the CGM consistently and the electronic data inform patient and clinician, then it is still useful and feasible. We will examine, analyze and report the data in its entirety, and compare to other studies.

Overall, I really like this study and believe that it addresses an important issue.

Reviewer: 3
Dr. Antoinette Moran, University of Minnesota System Comments to the Author:
Overall this is a worthy project in the effort to advance T1D control in Africa and other low resource countries. I just have a few minor comments:
1. Will insulin insecurity be a problem? They say nothing about how patients receive insulin.

All insulin at the clinics is always provided free of charge and provided at their routine monthly visits.. Insulin insecurity has not been a problem thus far at the sites. We have added the following text on page 4:
“All insulin is provided free of charge to all patients at their monthly appointments”

2. I'm a little dubious of their sample size calculations given that they will include all subjects including new onset, who may have significant HbA1c drops as they enter the honeymoon. Nonetheless this this is a feasibility study so efficacy power is not so important.
We recognize the issues with sample size, and are including all patients enrolled at these two sites. As you say this is a feasibility study

3. How to they expect COVID-19 to impact study procedures and do they have a contingency plan? This study has already been delayed twice due to COVID, and travel related restrictions. if necessary we will delay again. Throughout the pandemic in-person care has not stopped for T1D patients, and we do not foresee that changing.
4. What about CGM time-in-range as an outcome? There are many factors that can cause spurious HbA1c results in Africa---sickle cell disease/trait, iron deficiency, chronic malaria, etc.
As we already note on page 7, time in range is a secondary outcome. We state on page 6 “While percent time in range is considered the gold standard in CGM trials, because in this trial we are unsure what proportion of individuals will be able to successfully use their CGM, we are choosing HbA1c as a primary outcome, as we will be able to measure it in all study participants. “

VERSION 2 – REVIEW

REVIEWER	Black, Sheila University of Alabama, Psychology
REVIEW RETURNED	05-Jan-2022

GENERAL COMMENTS	The authors have addressed my concerns

REVIEWER	Moran, Antoinette University of Minnesota System
REVIEW RETURNED	27-Dec-2021

GENERAL COMMENTS	I am satisfied with the revisions. Good luck with the project!