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Randomized control trial for the feasibility of continuous glucose monitoring in patients with type 1 diabetes at two district hospitals in Neno, Malawi.

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ABSTRACT

Objectives: To assess the feasibility and clinical effectiveness of Continuous Glucose Monitoring (CGM) use among a rural population in Malawi living with type 1 diabetes
Design: a 2:1 open randomized controlled feasibility trial
Setting: Two Partners In Health-supported Ministry of Health-run first level district hospitals in Neno, Malawi
Participants: 45 people living with type 1 diabetes
Interventions: Participants were randomly assigned to Dexcom G6 CGM (n=30) use or usual care (UC) (n=15) consisting of Safe-Accu glucose monitors and strips. Both arms received diabetes education.
Outcomes: Primary outcomes included fidelity, appropriateness, change in HbA1c, and severe adverse events. Secondary outcomes included acceptability, time in range (CGM arm only) standard deviation of HbA1c, and quality of life.
Results: Participants tolerated CGM well but were unable to change their own sensors which resulted in increased clinic visits in the CGM arm. Participants in the CGM arm had greater numbers of dose adjustments and lifestyle change suggestions than those in the UC arm. There was a trend towards reduction of HbA1c in the CGM arm (-1.1% 95%CI -2.4, 0.3). Participants in the CGM arm wore their CGM on average 63.8% of the time. Participants in the UC arm brought logbooks to clinic 75% of the time. There were three hospitalizations all in the CGM arm, but none were related to the intervention.
Conclusions: This is the first RCT conducted on CGM in a rural region of a low-income country (LIC). CGM was feasible and appropriate among PLWT1D and providers, but inability of participants to change their own sensors is a challenge.
Trial registration: Trial registration number PACTR202102832069874. This study was approved by National Health Sciences Research Committee of Malawi (IRB Number IR800003905) and the Mass General Brigham (IRB number 2019P003554). The protocol was previously published(1).

Strengths and limitations of this study:

1. The first RCT evaluating feasibility and acceptability of CGM in a rural, low-literacy population in a low-income country
2. Study participants were followed for a period of 90 days, allowing for longitudinal data on impact of CGM
3. Limited by small sample size

Keywords: Type 1 diabetes, Continuous glucose monitoring (CGM), Self-monitoring, technology, feasibility study, RCT, Low income countries.

INTRODUCTION

Type 1 diabetes (T1D) is a severe autoimmune condition which leads to hyperglycemia and a lifelong insulin dependency(2). People living with type 1 diabetes (PLWT1D) require uninterrupted access to insulin, tools for glucose monitoring, and continuous access to education and healthcare services to reduce the risk of mortality, adverse events, and long-term complications. In low-income countries (LICs) and lower-middle-income countries (LMICs) access to affordable and high-quality care is limited. T1D incidence and mortality in these settings are likely underestimated as misdiagnosis and non-diagnosis are common(3-6). Without adequate care, the life expectancy of a child with newly diagnosed T1D in most LICs might be as short as one year(7, 8). Evidence suggests that currently, almost 9 million individuals are living with T1D, of which one-fifth (1,665,997 people) are in LICs and middle-income countries(9). In Malawi, 6,530 people were estimated to be living with T1D in 2022 (9). Given these current estimates, it is imperative to improve diabetes care in these settings with integrated care delivery, education, and training.

An intermediate level of care for T1D (defined as multiple daily injections of insulin, self-monitoring of blood glucose (SMBG) 2–4 times per day, consistent point-of-care hemoglobin A1c (HbA1c), complication screening, and a team approach to diabetes education and support) is an achievable goal for resource-limited settings that could decrease complication rates and premature mortality (10).

SMBG has improved clinical outcomes and quality of life for PLWT1D and was the gold standard of care following the Diabetes Control and Complications Trial (DCCT)(11). Novel technological advances for glucose monitoring are now available, requiring an interstitial patch and a reader for real-time continuous glucose monitoring (CGM) using Bluetooth technology. Products including Dexcom G6 (Dexcom, Inc., San Diego, CA, USA) have reduced the burden of finger sticks by providing interstitial glucose readings, trends, and alerts in real-time with a significant reduction in the frequency of severe hypoglycemic episodes(12).

CGM addresses many limitations related to HbA1c testing and SMBG. HbA1c gives only a point estimate of the mean of blood glucose control. SMBG gives some information on variability but not a complete picture, and neither provide real-time alerts about hypo- or

hyperglycemia. The uptake of CGM devices in many high-income countries (HICs) is gradually increasing, with good acceptability and clinical outcomes. A recent international consensus statement on the use of CGM technology concluded that CGM data should be used for therapeutic treatment decisions related to hypoglycemia and glucose variability (13).

Currently, no data exist on the feasibility and clinical impact of CGM for PLWT1D in rural areas of LICs especially in areas without electricity, and having low literacy and numeracy. To address this lack of evidence, we conducted a randomized trial to evaluate the feasibility of CGM technology and clinical impact among PLWT1D with limited literacy receiving diabetes care at two district hospitals in rural Malawi. This study is approved by National Health Sciences Research Committee of Malawi (IRB Number IR800003905) and the Mass General Brigham (IRB number 2019P003554). The protocol was previously published(1).

OBJECTIVES

The objectives of this study are to (1) assess the feasibility and appropriateness of CGM use among a rural population of PLWT1D and limited literacy in an LIC; (2) to determine the effectiveness of CGM on diabetes clinical outcomes among PLWT1D in LICs using clinical endpoints and (3) determine the standard deviation of HbA1c across individuals to inform further studies.

METHODS

Study setting

The study was conducted at two rural Ministry of Health (MOH) supported first-level hospitals in Neno district, Malawi, with a population of about 138,000(14), primarily relying on subsistence agriculture. Neno District Hospital is in a mountainous region near the Mozambique border and Lisungwi Community Hospital is in the lower, drier area near the Shire River. Both hospitals are similar in protocol and resources and are overseen by the same district leadership. Since 2007, Partners In Health (PIH), a US-based non-government organization known locally as Abwenzi Pa Za Umoyo (APZU), has partnered with MOH to improve healthcare and socioeconomic development in Neno District. In 2018, two advanced non-communicable disease (NCD) clinics providing high-quality care for complex NCDs, consistent with the Package of essential medicines for noncommunicable diseases-Plus (PEN-

Plus) opened at Upper Neno and Lisungwi(15-17). Patients with T1D enrolled in this clinic receive care from mid-level providers with specialized non-communicable disease (NCD) training. All insulin, syringes, and tools for SMBG are provided free of charge to all patients at their routine monthly appointments. Every household in Neno is visited by a community health worker (CHW) monthly for education and screening for multiple common conditions, enrolment into maternal and chronic care, and accompaniment to the clinic(18).

Study Participants

Eligibility criteria for this study included a clinical diagnosis of T1D from any age group, in diabetes care for at least one year, and seeking care at either of the PIH-supported MOH hospitals. Exclusion criteria included pregnancy, mental impairment, and the inability of the subject or care provider to use a CGM device. Figure 1 shows the flow diagram of the recruitment process.

Each participant was required to complete an informed consent/ assent (children <18 years of age) form on the day of the enrolment. Study staff were trained to assist patients with limited literacy with the consent process.

Design

Randomization

All 45 participants known to have T1D and seeking care at hospitals in Neno met the study criteria and were approached for willingness to participate in this study. All agreed and were randomly assigned via a random numbers table to either of the two arms: CGM (Dexcom G6, Dexcom, Inc.) arm and usual care arm (using blood glucose meter) in a 2:1 ratio. Study investigators and personnel were masked to the randomization sequence which was created by a senior researcher.

Provider training

Clinical providers were required to complete one month of virtual training on routine diabetes care and understanding CGM in the management of diabetes performed by the study team

(including two nurse practitioners and one physician trained in T1D care). Then, providers completed a two-week in-person hands-on training where they were required to wear a CGM and learn how to use Clarity (Dexcom CGM software). Providers were trained to review data from CGM downloads and SMBG logbook data and make individualized dose adjustments, changes in alarm alerts on the CGM reader, and recommendations for lifestyle and insulin dosing as per usual practice. Clear protocols warranting medical attention were supplied to the providers, and any reported adverse events were immediately assessed and documented. Provider training focused on: glucose targets; goal of time in range (TIR), insulin dosing techniques and principles; basics of insulin therapy and meal planning; understanding signs and strategies for managing hypoglycemia and hyperglycemia; understanding sick day management; understanding food insecurity and insulin dose adjustments; and troubleshooting common problems with Dexcom devices.

Intervention

Participants in the CGM arm were provided with a transmitter, a receiver, and sensors (Dexcom G6) inserted under the skin using an applicator to wear real-time continuous glucose monitoring technology for three months. All CGM equipment was provided free by Dexcom. Each transmitter had a shelf life of 90 days and each sensor had a shelf life of 10 days after which a new sensor needs to be applied. Participants in the CGM arm were instructed to use CGM daily and were advised to either change the sensor on their own or follow up after ten days for new sensor insertion. Individualized clinical recommendations were made by their providers at each visit using standardized material developed for the study based on Dexcom training materials (Appendix A). Participants in the CGM arm received a Chichewa-language handout at the beginning of the study to educate them about the features of CGM and readings obtained from the reader.

Comparator

Participants in the usual care arm were asked to perform home blood glucose monitoring using Safe Accu glucose meters and test strips at least once daily and record in the logbooks as per established protocol(19). Providers were encouraged to review retrospective glucose

data using SMBG logbook with participants and use the data to adjust insulin and lifestyle recommendations for individualized management.

Both Arms

The study staff provided guidelines for routine diabetes management and education to participants in both arms. Follow-up visits for both arms occurred monthly on the usual clinic schedule. The CGM group had additional visits for new sensor insertion and data downloads. Study staff had phone calls with participants to review for any severe adverse events during the study. Participants in both groups received financial compensation for travel to the clinic for each study visit. All diabetes and testing materials were provided free to all participants.

Data collection and interviews

Quality of life and HbA1c were measured at baseline and the end of the study using the WHO Quality of Life questionnaire and a point of care HbA1c testing device, respectively. At each visit, logbooks for those in the usual care arm and Clarity reports for those in the CGM arm were reviewed. Five participants from each arm were interviewed by the study staff at baseline and endline to discuss their satisfaction with content, use, complexity, comfort, and challenges of CGM and glucose meter technology in their setting. Five providers were interviewed regarding their opinions on both technologies. The recruitment of study participants began in March 2022 and data collection was completed by July 2022.

Outcomes

Primary outcomes were split into implementation outcomes, defined using the Proctor (20) framework, and clinical outcomes.

Implementation outcomes

Fidelity

Fidelity is defined here using variables reflecting patients' adherence to the technology used(20). In the CGM arm, fidelity was defined by number of sensors worn, the percent of

time sensors were worn (based on Clarity reports), and times that dose or lifestyle adjustments were made. In the usual care arm, fidelity was defined as the percent of expected blood glucose readings logged, the percent of participants who brought logbooks to the clinic during the study period, percent of expected times blood glucose test was performed, the number of times insulin adjustments were made, and how often lifestyle adjustments were suggested.

Appropriateness

Appropriateness was defined as the perceived fit and relevance or compatibility of CGM(20). This was based on sensor problems, reporting of technological issues, and qualitative interviews.

Clinical outcomes

Change in HbA1c

Change in Hba1c was measured as the change from baseline to endline measured using PTS diagnostics A1CNow+ point of care test kits.

Severe adverse events

Severe adverse events were measured from patient self-reports, CGM or home glucose meters, or clinician reports.

Secondary outcomes

Implementation outcomes

Acceptability was defined using Proctor's framework as the perception that CGM was agreeable, palatable, or satisfactory (20). This was measured through qualitative interviews with PLWT1D and providers.

Clinical outcomes

We were only able to measure TIR in the CGM arm, which was calculated using downloaded CGM data. We defined "in range" as blood glucose reading between 70 mg/dL and 180 mg/dL(21). "Very high" was defined as over 250 mg/dL, and "very low" as below 54 mg/dL.

Because two participants only had fewer than five days of CGM readings each, we included a sensitivity analysis removing these participants' data.

The standard deviation in HbA1c was calculated using the overall HbA1c SD in the baseline point-of-care tests. Quality of life (QoL) was measured using the WHO-BREF both at baseline and at the end of the study. The WHO-BREF includes four domains: Physical health, psychological, social relationships, and environment. QoL was calculated both by individual domain and overall.

Statistical methods

Statistical analyses were conducted using R version 4.2.2, or Stata version 14. We included the entire population of PLWT1D receiving care at two PIH assisted hospitals, so no sample size calculations were conducted. Power was calculated for detecting the difference in HbA1c—given an overall standard deviation of 2.05, we were only powered (80%) to detect a 1.5% difference between the two study arms. We conducted analysis as intention to treat.

HbA1c analysis

To test whether the change in HbA1c differed between the CGM and usual care arms, we used longitudinal analysis of covariance—equivalent to the linear regression model specified below, where HbA1c at follow-up ($HbA1c_{t1}$) is predicted by study arm (SA), HbA1c at baseline ($HbA1c_{t0}$), facility site (Site), age (Age), female gender (Fem), diagnosis year (DY), and body mass index (BMI). The coefficient on study arm, $\boldsymbol{\beta_1}$, was the parameter of interest.

$$HbA1c_{t1} = \beta_0 + SA\boldsymbol{\beta_1} + HbA1c_{t0}\beta_2 + Site\beta_3 + Age\beta_4 + Fem\beta_5 + DY\beta_6 + BMI\beta_7 + \varepsilon$$

We report the point estimate and 95% confidence interval for this parameter estimate from the fully adjusted model above as well as a minimally adjusted model, only including the terms for study arm and baseline HbA1c.

Quality of life analysis

To estimate the difference in the change in QoL between study arms, we used the same approach as for HbA1c. We conducted a regression for each of the four domains of the WHO-BREF as well as the overall score, reporting the point estimate and 95% confidence

interval for the estimated difference in the change between the arms from the fully adjusted model, adjusting for the same variables as in the HbA1c analysis described above except for BMI.

Percent of time worn and time in range analyses

This CGM device measures glucose levels roughly every five minutes. We summarized the measurements in several ways. First, we calculated the proportion of expected observations that were missing values. We did this by dividing time into five-minute increments. If no observation was present for a period longer than 5.06 minutes, we considered each five-minute increment between the previous and subsequent observations as missing. Then, we calculated the proportion of all observations that were missing. We calculated the proportion of non-missing observations within the desired blood glucose range (70 to 180 mg/dL) to estimate time in range, as well as the proportion that were very low (under 54 mg/dL), low (54 mg/dL to 69 mg/dL), high (181 mg/dL -250 mg/dL), and very high (over 250 mg/dL). We additionally calculated the mean and interquartile range of the non-missing observations.

The CGM sensors lasted 10 days, but many patients returned to the clinic every 14 days to obtain replacement sensors. Therefore, a substantial proportion of the missingness was related to timing of sensor replacement. We estimated this proportion by assuming that any missingness on the day of a sensor replacement (recorded by study clinicians) was related to the replacement, and any missingness contiguous with (i.e., no non-missing observations between) and prior to (including in previous days) that period of missingness was categorized as related to the sensor replacement. We then tabulated the proportion of missing observations related to sensor replacement. Not all individuals experienced long periods missing a sensor, as some felt comfortable replacing sensors at home and were given extra sensors by study staff.

Qualitative methods

We conducted a series of semi-structured interviews with 10 patients (five in each arm) at the beginning and end of the study. We also interviewed five providers (two nurses and three

clinicians) who provided care to the patients during the study period. Trained members of the study team conducted all interviews. Provider interviews were conducted in English. Patient interviews were conducted in Chichewa, and translated by a bilingual researcher. All interviews were audio recorded and transcribed by a trained researcher. Interviews were coded in Dedoose and analyzed using a thematic framework using a-priori themes.

Deviations from protocol

We initially planned a two-day training for participants, with one day devoted to comprehensive T1D education. However, due to long distances needed to travel for participants and resulting missed school and work, two consecutive days was not feasible. Instead, for two months before the start of the study, providers gave enhanced diabetes education to all participants. In the protocol outcomes, we had stated the percent of expected times CGM and SMBG information was used to inform lifestyle-adjusted interventions, and we were unable to determine the percent so we used number of times instead.

Patient and public involvement

PLWT1D were engaged throughout the study. Three of the outcomes of this research were feasibility, acceptability, and appropriateness, so much of the study involved gaining perspectives, experiences and views of the technology by PLWT1D. Two of the study coauthors (GF & AG) are living with T1D, and were involved throughout the design of the protocol, tools, training and implementation of the study.

RESULTS

Participants

There were 45 individuals with T1D meeting the inclusion criteria at the two eligible hospitals. When approached by phone, all agreed to be included and were randomized, 30 to the CGM arm and 15 to the UC arm. On the day of trial initiation, one from the CGM arm and two from the UC arm did not present and therefore did not participate. At the end of the study, one participant in the CGM arm and two from the UC arm were not present for their final evaluations and were considered lost to follow-up (Figure 1). The trial was initiated on April 11th 2022 in Lisungwi district hospital and April 14th 2022 in Upper Neno

district hospital and ran for 90 days. Table 1 shows baseline characteristics of trial participants in both arms.

Table 1: Characteristics of participants at baseline

		Study arm	
		CGM (N=29)	*Usual care (N=13)*
Location (% Upper Neno)		48.0	46.0
Age (years) (mean (range))		30.9 (8, 51)	29.6 (8,46)
Sex (%)			
	Female	48.0	38.0
	Male	52.0	62.0
Year of diagnosis (mean (SD))		2016 (6.1)	2018 (1.6)
Median year of diagnosis		2018	2018
BMI (mean (SD))		21.4 (3.6)	24.5 (5.6)
Baseline HbA1c (%) (mean (SD))		8.5 (2.2)	7.9 (2.1)
Baseline total daily insulin dose (units/day)		53.59	49.23

*CGM: Continuous Glucose monitoring, SD: Standard deviation

Primary Outcomes

Implementation outcomes

Fidelity

Major fidelity outcomes are seen in Table 2 and Figure 2. There was a higher rate of consultations in the CGM arm (mean 8.3) compared to the usual care arm (1.3). In the CGM arm, participants used a mean of 6.8 sensors over the study period, with a range of 2 to 9 sensors. The average participant had recordings taken by their sensors for 63.8% of the time (median: 65.5%, interquartile range: 49.9-75.6%). A sensitivity analysis done dropping two individuals with only two days of observation made little change to the result (average 63.5% median: 65.5% IQR 49.3-t5.7%). As many participants were unable to change the sensor on their own, and clinic days were only once a week, there was, on average, a four-day lag between one sensor ending and the next sensor being applied. We estimated the amount of each individual's missingness due to this four-day lag and found that, on average, 72.7% of the missingness was due to lags between sensor changes (median: 83.4%,

interquartile range (IQR): 63.7%-92.6%)). Sensitivity analysis showed only minimal change to the result (mean 74.4%; median 83.4%, IQR: 65.1%-92.6%)). Among the time we did not classify as "missing due to sensor change" because of missingness adjacent to documented sensor changes, participants had sensor recordings an average of 87.0% of the time (sensitivity analysis 86.9%).

Table 2: Measures of fidelity in participants

	Study arm	
	CGM (N=29)	*Usual care (N=13)*
Consultations attended (mean)	8.3	1.3
Individuals with insulin adjustments (n (%))	20.0 (69.0)	2.0 (15.0)
Insulin adjustments made (n)	35.0	2.0
Insulin adjustments per individual (mean)	1.2	0.2
Lifestyle change suggestions (n)	13.0	3.0
Lifestyle change suggestions per individual (mean)	0.4	0.2
CGM arm		
Sensors worn, mean (range)	6.8 (2,9)	
Percent of time worn, mean (SD)	63.8 (16.1)	
Usual care arm		
Consultations with logbook brought to clinic (%)	75.0	
Readings logged (%)	51.3	

*CGM: Continuous glucose monitoring, SD: standard deviation.

In the usual care arm, participants brought logbooks to consultations 75% of the time. However, readings in logbooks corresponded to glucose meters readings only 51.3% of the time.

Of the 29 individuals in the CGM arm, 20 (69%) had an insulin adjustment made, compared with only two individuals (15%) in the UC arm. There were a total of 35 insulin adjustments in the CGM arm, which came to an average of 1.2 per individual, compared to 0.2 per individual in the UC arm. There were roughly double the amount of suggested lifestyle changes in the CGM arm (0.4 per person) compared to the UC arm (0.2) (Table 2).

Appropriateness

Over the course of the trial, only one participant in the trial arm was able to change the sensors himself. Two others felt confident to physically change the sensor but were unable to enter the code, so they still needed to come into the clinic to change the sensor. Clinicians reported that after multiple CGM insertions, patients felt confident with the application process and were able to self-apply with guidance, however they were unable to correctly input the sensor codes. In total, there were 28 cases of sensor failure over the three-month trial period. During the first sensor use, three individuals complained of discomfort but worked with providers to find a more comfortable way of wearing them. In the first month, three participants accidentally removed the sensors, but there were no reported cases after the first month. There were no reported problems with the solar chargers, and participants were able to use the solar chargers for light in their houses.

Clinical outcomes

After three months, we observed an increase of 0.2 percentage points in HbA1c in the usual care arm (N= 11 as follow-up HbA1cs missing for two participants) and a reduction of 1.2 percentage points in the CGM arm (N=28) compared to baseline. After adjusting for baseline HbA1c levels and other covariates, there was a non-significant trend towards participation in CGM leading to a greater reduction in HbA1c (1.1 percentage points; 95% CI: 2.4 percentage point reduction to 0.3 percentage point increase) compared to usual care (Table 3). Throughout the study there were three hospitalizations in the CGM arm and none in the usual care arm. None of the hospitalizations were attributed to the intervention. One was due to a long-standing non-healing diabetic foot issue, one was due to low blood sugar due to the participant having no food, and one was due to high blood glucose levels.

Secondary Outcomes

Overall, participants and providers found the CGM devices acceptable. The main reported complaints concerned the length of time that sensors lasted, and the alarms on the CGM monitors, and some participants reported not liking the visual aspect of the sensor. We go further into qualitative outcomes in our companion piece(22).

The average percent TIR in recorded readings (not including missing data) was 30.6% (SD 16.1%) (Figure 2). Among the 27 CGM arm participants with more than one week of recorded data, the average TIR was 32.6% (SD 14.7%). Over the course of the study, there was an increase in the time in the range starting in week 6 (Supplementary Figure 1). The average time in range was 30.8% in week 1, and 38.7% in week 10. To test if this increase in TIR was due to drop off of non-compliant participants, we conducted a sensitivity analysis looking at only participants who we had data for at 10 weeks. Among the 20 participants with greater than 5% non-missing data in week 10, the average time in range in week 1 was 34.5%, and the average in week 10 was 37.5% (Supplementary Figure 1).

Pretrial, there was an average standard deviation of 2.1 in HbA1c across two arms (Table 3), although baseline HbA1c was low overall compared to what is generally expected in this type of setting(23-25).

Table 3: Change in HbA1c at three months

	Arm		Mean difference (95% CI)	P- value
	CGM (N=28) Mean (SD)	**UC N=11 Mean (SD)**		
HbA1c at follow-up	7.4 (1.9)	7.9 (2.0)		
Crude change from baseline	-1.2 (1.9)	0.2 (2.7)	-1.38 (-2.92, 0.17)	0.08
Model 1			-0.88 (-2.15, 0.40)	0.17
Model 2			-1.07 (-2.39, 0.26)	0.11

Model 1 adjusted for baseline HbA1c only; Model 2 adjusted for baseline HbA1c, facility site, age, sex, diagnosis year, and BMI. Note: 28 of the original 29 were included from the CGM arm because 1 person did not have a follow-up HbA1c measurement, and 11 of 13 were included in the usual care arm because of missing follow-up measures.
CGM: Continuous Glucose monitoring, CI: Confidence interval, SD: standard deviation

Over the course of the study, QoL (N=28 in CGM and N=10 in UC) was assessed using WHO-BREF increased across all domains (Supplementary Table 1), but there was no statistically significant difference between change in arms, although unadjusted QoL increased slightly more in the UC arm (9.0) than the CGM arm (6.7).

DISCUSSION

Summary of main results

This is the first RCT to be carried out in a rural area of a LIC on the feasibility of CGM. While participants wore their sensors just under two-thirds of the time, much of the missingness (over 70% on average) was attributable to their inability to change their sensors. The most pervasive barrier to CGM use among patients was the reported limited digital literacy and confidence with the sensor application process, which required patients in the CGM arm to come more frequently into the clinic than the usual care arm. However, with time and multiple CGM insertions, patients felt confident with the application process and could self-apply under the guidance of the clinicians, but still needed help with numerically entering sensor codes to activate them. After the first few weeks, participants tolerated the CGM well, and clinicians were far more likely to make dose adjustments in the CGM arm than the usual care arm. There was a trend towards greater reduction in HbA1C in the CGM arm than in the usual care arm. However, there were many more consultations in the CGM arm, so it is difficult to attribute the improvement to the CGM or the greater number of consultations. Given the four-day lag between sensor end and replacement, the reduction may have been greater without this lag.

Comparisons with other studies

This is the first RCT conducted in a rural setting in a LIC to assess the feasibility of CGM and its effect on clinical outcomes and quality of life among people living with T1D. To date, there are less than a handful of studies on CGM use in the African continent, none of which are randomized control trials. One of these studies evaluated the glycemic profile – glucose exposure, variability, stability, and risk of hypoglycemia – of people living with T1D and T2D in South Africa, across 16 different clinics(26). In Uganda, Niwaha and colleagues conducted a study to assess the risk of hypoglycemia for people living with T2D being treated with sulphonylureas or insulin and did not include PLWT1D(27). While the study in South Africa mentioned that some sensors failed to record data, neither this study nor that of Niwaha looked specifically at fidelity, appropriateness, or acceptability. A short observational study by McClure Yauch and Velazquez (2020) was conducted at national referral hospitals in urban areas in Kenya and Uganda to assess feasibility of CGM use and the glycemic profile of

children and young adults affected by T1D using CGM technology (28). They found the use of this technology was tolerated by patients and expressed hope for wider use in the future. This urban study reported an average HbA1c of 10.9% with a SD of 2.7 compared to our average baseline HbA1c of 8.3% and endline HbA1c of 7.5% with a SD of 2.1. Their TIR was 31% compared to the TIR in our study of over 37% by week 10 (32.6% across the whole study period among the 27 participants in the CGM arm with more a few days of data). All three of these studies used the Freestyle Libre Pro, and users were blinded to their glucose data and had CGM use of 14 days. In our study we used the Dexcom G6 CGM for 90 days, which provides real-time glucose data to the user and can be used to make treatment decisions. None of these studies examined any association between CGM use and QOL.

Despite challenges participants experienced with changing sensors and data missingness, the amount of glucose data recorded from sensor readings in this study - 63.8% of the time (median: 65.5%, interquartile range: 49.9-75.6% sensitivity analysis is mean: 63.5%; median: 65.5%; IQR; 49.3-75.7%.) and 87% when excluding missingness due to lag in sensor change – is higher than data from sensor readings [mean of 51.14 days (60.9%) (*SD* = 20.86), range 20–81 days] in a 90-day pre- and posttest pre-experimental study with children, adolescents, and young adults with poorly controlled diabetes living in the U.S.(29). This underscores the importance, benefits, and potential for high impact of ensuring access for glucose monitoring devices for PLWT1D in low-resources settings.

Limitations

This was a feasibility trial with only 42 individuals, so may not have been powered for seeing differences between study arms. Due to the inability of patients in the CGM arm to change their device sensor, many patients ended up seeing providers twice a month compared to once a month in the usual care arm, making it difficult to separate effects of technology versus the effect of the increased frequency of visits. Additionally, providers were excited about the new technology and may have paid greater attention to patients in the CGM arm. All participants in the study had a diagnosis of T1D, however, limited resources and a lack of pancreatic antibody and c-peptide testing may mean some patients were misdiagnosed. This study was conducted for three months. While this is far longer than other studies,

reduction in HbA1c levels and behavior change can take longer than three months, so a longer study may have found greater effects. Conversely, we do not know what adherence would look like after three months.

Implications for future research and practice

Our study suggests that CGM is feasible, appropriate, and acceptable in rural Malawi, and may show greater effectiveness in lowering HbA1c than SMBG. We highlight the need to include practical digital literacy and numeracy training for patients when considering CGM as a viable clinical option in diabetes management in such settings, and future studies and practice should explore ways participants with low literacy can learn to change sensors independently. Newer models of CGM (Dexcom G7, Freestyle Libre 2 and Freestyle Libre 3) do not require sensor codes to be inputted for activation, so may be better suited to this setting. As devices were donated by Dexcom, this study did examine costs, but continued global advocacy is necessary to ensure equitable access to intermediate T1D care for PLWT1D in LICs. Other studies may examine if short periods of intensive CGM use are equally effective as a training tool for both patients and providers allowing a more granular assessment of glycemic control than previously possible with glucose meters. In contrast, other studies looking at longer lengths of time using CGM may be able to explore if this is a tool that can enhance PLWT1D's understanding of their condition, improve diabetes self-management, decrease adverse events and diabetes-related complications, advance providers' skills and knowledge, and assist with decision-making around insulin initiation for people living with type 2 diabetes. Further, examining if there is added benefit and cost effectiveness of real-time CGM compared to flash glucose monitoring and un-blinded CGM compared to blinded in this setting is warranted.

CONCLUSION

This is the first RCT conducted on CGM in a rural region of a LIC. Overall, this small feasibility study conducted in one Malawian district found CGM to be feasible and appropriate among PLWT1D and their health care providers. Inability of participants to change their own sensor is the biggest challenge, though could be addressed with use of newer sensor models. Although not statistically significant, the downward trend in HbA1c in

study arm is promising and worth investigating over a longer period, especially in light of increased TIR from baseline to endline. The current model of care needs to be strengthened and TIR continues to be low — posing higher risk for acute and chronic complications among this population.

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CONTRIBUTIONS

Study and tool design: AJA, TR, FV, CT, GF, AM, EW, CK, GB, PP.

Training: AG, CT, GF

Data analysis: MMC, FV, AG, AJA, AT, LD

All authors contributed to the final manuscript

GB, TR, and AJA share senior authorship.

COMPETING INTERESTS

The authors have no competing interests.

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Figure 1. Consort Study Flow Diagram

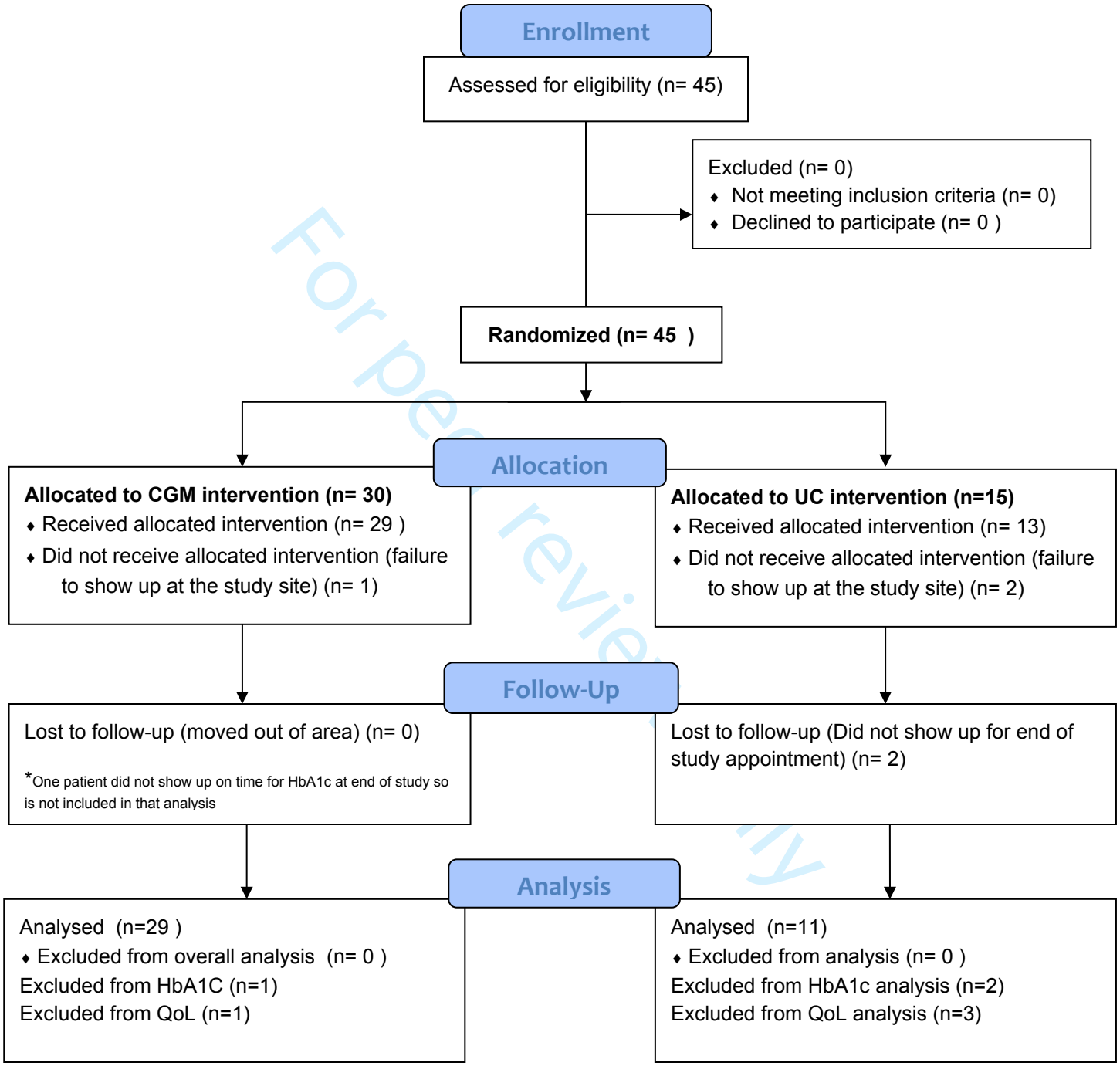
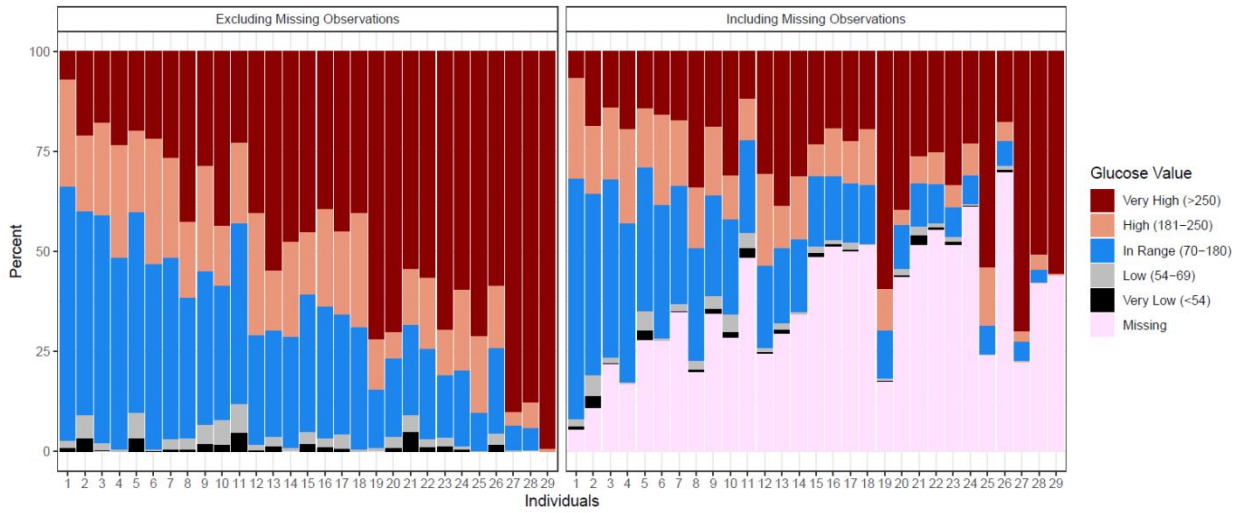


Figure 2. Time in range for each participant with missing data included and not-included



Note: Individuals 27 and 29 used CGM devices for less than one week.

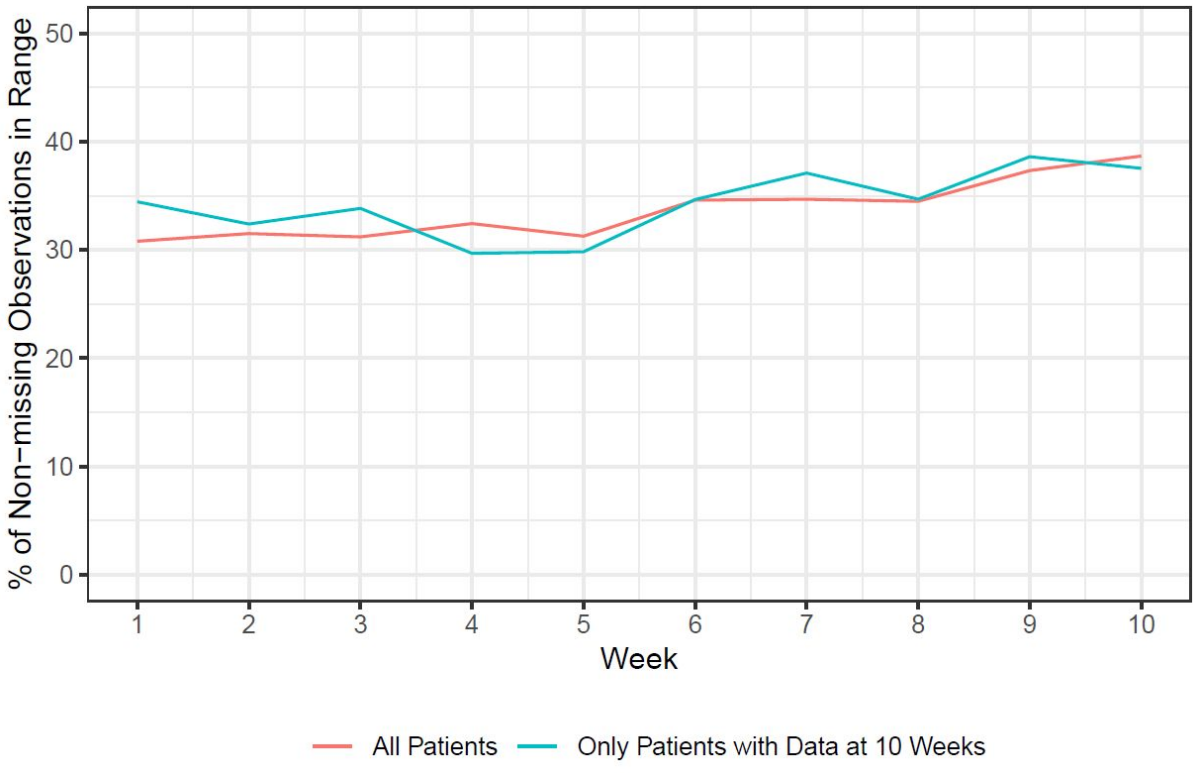
Supplementary Table 1: Quality of Life

	Crude			Adjusted Model		
	Pretest Mean (SD)	**Post test Mean (SD)**	**Difference**	**Coefficient**	**95% CI**	**P-value**
Domain 1: Physical health						
CGM	53.5 (13.1)	55.1 (14.6)	1.6	-4.32	-14.9, 6.2	0.41
UC	50.2 (18.4)	57.0 (9.1)	6.8			
Domain 2: Psychological						
CGM	53.2 (13.1)	57.6 (17.7)	4.4	0.36	-11.3, 12.6	0.95
UC	54.5 (15.5)	57.0 (18.0)	2.5			
Domain 3: Social relationships						
CGM	46.0 (17.9)	58.5 (23.3)	12.5	-8.94	-25.5, 7.6	0.28
UC	47.3 (29.9)	67.5 (20.5)	20.2			
Domain 4: Environment						
CGM	47.4 (16.3)	55.5 (17.1)	8.2	-0.84	-11.9, 10.2	0.88
UC	52.6 (18.7)	58.9 (21.2)	6.3			
Overall						
CGM	50.0 (12.5)	56.7 (15.6)	6.7	-3.75	-13.7, 6.2	0.45
UC	51.2 (16.7)	60.1 (14.7)	9.0			

Note: There were 28 participants in the CGM arm and 10 in the usual care arm (1 and 3 of the original participants with no follow-up data in the respective arms). Coefficient, 95% CI, and p-value reported from longitudinal analysis of covariance, adjusted for baseline quality of life score, facility site, age, gender, and diagnosis year.

CGM: Continuous Glucose monitoring, CI: Confidence interval, SD: standard deviation

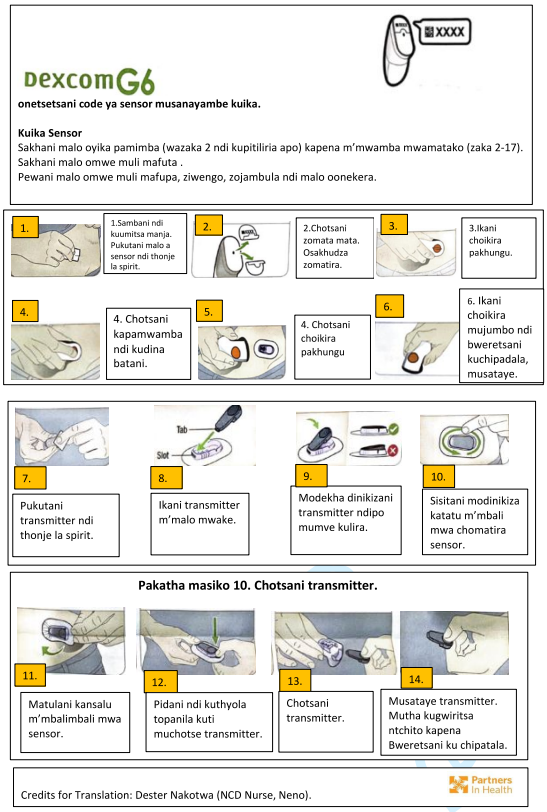
Supplementary Figure 1: Average time in range over course of ten weeks for participants with data at ten weeks



Appendices

Appendix A

Dexcom patient handout (English and Chichewa versions used during the study)



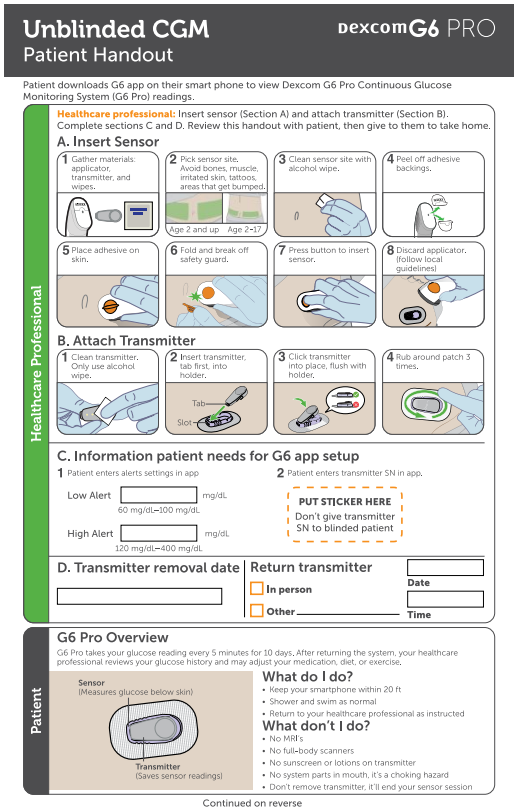


Table A : Training of participants performed in both arms and guidelines for clinicians

Participant Training at Baseline (For both groups): One session of general diabetes education and management

- Glucose targets
- Insulin dosing techniques and principles
  - Take before, not after each meal
  - Do not skip doses
- Basics of insulin therapy and meal planning
- Understanding signs and strategies for managing hypoglycemia and hyperglycemia
- Understanding sick day management.
- Understanding food insecurity and insulin therapy.

Clinician Guidelines:

- Providers were encouraged to review retrospective glucose data using SMBG logbook and CGM Clarity reports with participants and use the data to adjust insulin for individualized management.
- Make lifestyle and medication/insulin recommendations ***per usual practice***
- For CGM Group—CGM diabetes management guidelines

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of study as randomised pilot or feasibility trial	1
Authors *	Contact details for the corresponding author	31
Trial design	Description of pilot trial design (eg, parallel, cluster)	50
Methods		
Participants	Eligibility criteria for participants and the settings where the pilot trial was conducted	152-179
Interventions	Interventions intended for each group	208-237
Objective	Specific objectives of the pilot trial	141-146
Outcome	Prespecified assessment or measurement to address the pilot trial objectives**	252-307
Randomization	How participants were allocated to interventions	183-189
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	50
Results		
Numbers randomized	Number of participants screened and randomised to each group for the pilot trial objectives**	386-387
Recruitment	Trial status†	
Numbers analysed	Number of participants analysed in each group for the pilot objectives**	447,480-482,401
Outcome	Results for the pilot objectives, including any expressions of uncertainty**	401-496
Harms	Important adverse events or side effects	453
Conclusions	General interpretation of the results of pilot trial and their implications for the future definitive trial	588-598
Trial registration	Registration number for pilot trial and name of trial register	70
Funding	Source of funding for pilot trial	613-616

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

**this item is specific to conference abstracts*

***Space permitting, list all pilot trial objectives and give the results for each. Otherwise, report those that are a priori agreed as the most important to the decision to proceed with the future definitive RCT.*

†For conference abstracts.

BMJ Open

Randomized control trial for the feasibility of continuous glucose monitoring in patients with type 1 diabetes at two district hospitals in Neno, Malawi.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-075554.R1
Article Type:	Original research
Date Submitted by the Author:	23-Jan-2024
Complete List of Authors:	Gomber, Apoorva; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity Valeta, Francis; Partners in Health Coates, Matthew M.; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity Trujillo, Celina; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity; Partners In Health Ferrari, Gina; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity; Partners In Health Boti, Medson; Partners in Health Kumwenda, Kenwood; Partners in Health Mailosi, Bright ; Partners in Health Nakotwa, Dester; Partners in Health Drown, Laura ; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity Wroe, Emily B.; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity ; Partners In Health Thapa, Ada; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity Mithi, Victor; Partners In Health Matanje, Beatrice ; Partners In Health Msekandiana, Amos; Baylor College of Medicine; Kamuzu Central Hospital Park, Paul H; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity Kachimanga, Chiyembekezo; Partners In Health Bukhman, Gene; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity ; Partners In Health Ruderman, Todd; Partners in Health Adler, Alma; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity
Primary Subject Heading:	Global health
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES &

	ENDOCRINOLOGY, International health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Randomized control trial for the feasibility of continuous glucose monitoring in patients with type 1 diabetes at two district hospitals in Neno, Malawi.

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ABSTRACT

Objectives: To assess the feasibility and change in clinical outcomes associated with Continuous Glucose Monitoring (CGM) use among a rural population in Malawi living with type 1 diabetes **Design:** a 2:1 open randomized controlled feasibility trial
Setting: Two Partners In Health-supported Ministry of Health-run first level district hospitals in Neno, Malawi
Participants: 45 people living with type 1 diabetes
Interventions: Participants were randomly assigned to Dexcom G6 CGM (n=30) use or usual care (UC) (n=15) consisting of Safe-Accu glucose monitors and strips. Both arms received diabetes education.
Outcomes: Primary outcomes included fidelity, appropriateness, change in HbA1c, and severe adverse events. Secondary outcomes included acceptability, time in range (CGM arm only) standard deviation of HbA1c, and quality of life.
Results: Participants tolerated CGM well but were unable to change their own sensors which resulted in increased clinic visits in the CGM arm. Despite the hot climate, skin rashes were uncommon but cut-out tape overpatches were needed to secure the sensors in place. Participants in the CGM arm had greater numbers of dose adjustments and lifestyle change suggestions than those in the UC arm. There was a trend towards reduction of HbA1c in the CGM arm (-1.1% 95%CI -2.4, 0.3). Participants in the CGM arm wore their CGM on average 63.8% of the time. Participants in the UC arm brought logbooks to clinic 75% of the time. There were three hospitalizations all in the CGM arm, but none were related to the intervention.
Conclusions: This is the first RCT conducted on CGM in a rural region of a low-income country (LIC). CGM was feasible and appropriate among PLWT1D and providers, but inability of participants to change their own sensors is a challenge.
Trial registration: Trial registration number PACTR202102832069874. This study was approved by National Health Sciences Research Committee of Malawi (IRB Number IR800003905) and the Mass General Brigham (IRB number 2019P003554). The protocol was previously published.

Strengths and limitations of this study:

1. Randomized controlled trial evaluating feasibility and acceptability of CGM in a rural, low-literacy population in a low-income country
2. Study participants were followed for a period of 90 days, allowing for longitudinal data on impact of CGM
3. Limited by small sample size

Keywords: Type 1 diabetes, Continuous glucose monitoring (CGM), Self-monitoring, technology, feasibility study, RCT, Low income countries.

INTRODUCTION

Type 1 diabetes (T1D) is a severe autoimmune condition which leads to hyperglycemia and a lifelong insulin dependency(1). People living with type 1 diabetes (PLWT1D) require uninterrupted access to insulin, tools for glucose monitoring, adequate and uninterrupted access to needles and syringes, and continuous access to education and healthcare services to reduce the risk of mortality, adverse events, and long-term complications. In low-income countries (LICs) and lower-middle-income countries (LMICs) access to affordable and high-quality care is limited. T1D incidence and mortality in these settings are likely underestimated as misdiagnosis and non-diagnosis are common(2-5). Without adequate care, the life expectancy of a child with newly diagnosed T1D in most LICs might be as short as one year(6, 7). Evidence suggests that currently, almost 9 million individuals are living with T1D, of which one-fifth (1,665,997 people) are in LICs and middle-income countries(8). In Malawi, 6,530 people were estimated to be living with T1D in 2022 (8). Given these current estimates, it is imperative to improve diabetes care in these settings with integrated care delivery, education, and training.

An intermediate level of care for T1D (defined as multiple daily injections of insulin, self-monitoring of blood glucose (SMBG) 2–4 times per day, consistent point-of-care hemoglobin A1c (HbA1c), complication screening, and a team approach to diabetes education and support) is an achievable goal for resource-limited settings that could decrease complication rates and premature mortality (9).

SMBG has improved clinical outcomes and quality of life for PLWT1D and was the gold standard of care following the Diabetes Control and Complications Trial (DCCT)(10). Novel technological advances for glucose monitoring are now available, requiring an interstitial patch and a reader for real-time continuous glucose monitoring (CGM) using Bluetooth technology. Products including Dexcom G6 (Dexcom, Inc., San Diego, CA, USA) have reduced the burden of finger sticks by providing interstitial glucose readings, trends, and alerts in real-time with a significant reduction in the frequency of severe hypoglycemic episodes(11).

CGM addresses many limitations related to HbA1c testing and SMBG. HbA1c gives only a point estimate of the mean of blood glucose control. SMBG gives some information on variability

but not a complete picture, and neither provide real-time alerts about hypo- or hyperglycemia. The uptake of CGM devices in many high-income countries (HICs) is gradually increasing, with good acceptability and clinical outcomes. A recent international consensus statement on the use of CGM technology concluded that CGM data should be used for therapeutic treatment decisions related to hypoglycemia and glucose variability (12).

Currently, no data exist on the feasibility and effect on clinical outcomes of CGM for PLWT1D in rural areas of LICs especially in areas without electricity, and having low literacy and numeracy. To address this lack of evidence, we conducted a randomized trial to evaluate the feasibility of CGM technology and change in clinical outcomes among PLWT1D with limited literacy receiving diabetes care at two district hospitals in rural Malawi. This study is approved by National Health Sciences Research Committee of Malawi (IRB Number IR800003905) and the Mass General Brigham (IRB number 2019P003554). The protocol was previously published(13).

OBJECTIVES

The objectives of this study are to (1) assess the feasibility and appropriateness of CGM use among a rural population of PLWT1D and limited literacy in an LIC; (2) to determine if CGM use can have an effect on diabetes clinical outcomes among PLWT1D in rural regions of LICs and (3) determine the standard deviation of HbA1c across individuals at baseline to inform further studies.

METHODS

Study setting

The study was conducted at two rural Ministry of Health (MOH) supported first-level hospitals in Neno district, Malawi, with a population of about 138,000(14), primarily relying on subsistence agriculture. Neno District Hospital is in a mountainous region near the Mozambique border and Lisungwi Community Hospital is in the lower, drier area near the Shire River. Both hospitals are similar in protocol and resources and are overseen by the same district leadership. Since 2007, Partners In Health (PIH), a US-based non-government organization known locally as Abwenzi Pa Za Umoyo (APZU), has partnered with MOH to improve healthcare and socioeconomic development in Neno District. In 2018, two advanced

non-communicable disease (NCD) clinics providing high-quality care for complex NCDs, consistent with the Package of essential medicines for noncommunicable diseases-Plus (PEN-Plus) opened at Upper Neno and Lisungwi(15-17). Patients with T1D enrolled in this clinic receive care from mid-level providers with specialized non-communicable disease (NCD) training. All insulin, syringes, and tools for SMBG are provided free of charge to all patients at their routine monthly appointments. PLWT1D typically use human insulin, intermediate-acting (NPH) two times daily and fast- acting (regular) two to three times daily. Every household in Neno is visited by a community health worker (CHW) monthly for education and screening for multiple common conditions, enrolment into maternal and chronic care, and accompaniment to the clinic(18).

Study Participants

Eligibility criteria for this study included a clinical diagnosis of T1D in PLWT1D, in diabetes care for at least one year, and seeking care at either of the PIH-supported MOH hospitals. We did not exclude anyone based on age. Exclusion criteria included pregnancy, mental impairment, and the inability of the subject or care provider to use a CGM device. Figure 1 shows the flow diagram of the recruitment process.

Each participant was required to complete an informed consent/ assent (children <18 years of age) form on the day of the enrolment. Study staff were trained to assist patients with limited literacy with the consent process.

Design

Randomization

All 45 participants known to have T1D and seeking care at hospitals in Neno met the study criteria and were approached for willingness to participate in this study. All agreed and were randomly assigned via a random numbers table to either of the two arms: CGM (Dexcom G6, Dexcom, Inc.) arm and usual care arm (using blood glucose meter) in a 2:1 ratio. Study investigators and personnel were masked to the randomization sequence which was created by a senior researcher.

Provider training

Clinical providers were required to complete one month of virtual training on routine diabetes care and understanding CGM in the management of diabetes performed by the study team (including two nurse practitioners and two clinical officers trained in T1D care). Then, providers completed a two-week in-person hands-on training where they were required to wear a CGM and learn how to use Clarity (Dexcom CGM software). Providers were trained to review data from CGM downloads and SMBG logbook data and make individualized dose adjustments, changes in alarm alerts on the CGM reader, and recommendations for lifestyle and insulin dosing as per usual practice. Clear protocols warranting medical attention were supplied to the providers, and any reported adverse events were immediately assessed and documented. Provider training focused on: glucose targets; goal of time in range (TIR), insulin dosing techniques and principles; basics of insulin therapy and meal planning; understanding signs and strategies for managing hypoglycemia and hyperglycemia; understanding sick day management; understanding food insecurity and insulin dose adjustments; and troubleshooting common problems with Dexcom devices.

Intervention

Participants in the CGM arm were provided with a transmitter, a receiver, and sensors (Dexcom G6) inserted under the skin using an applicator to wear real-time continuous glucose monitoring technology for three months. All CGM equipment was provided free by Dexcom. Each transmitter had a shelf life of 90 days and each sensor had a shelf life of 10 days after which a new sensor needs to be applied. Participants in the CGM arm were instructed to use CGM daily and were advised to either change the sensor on their own or follow up after ten days for new sensor insertion. Individualized clinical recommendations were made by their providers at each visit using standardized material developed for the study based on Dexcom training materials (Appendix A). Participants in the CGM arm received a Chichewa-language handout at the beginning of the study to educate them about the features of CGM and readings obtained from the reader.

Comparator

Participants in the usual care arm were asked to perform home blood glucose monitoring using Safe Accu glucose meters and test strips at least once daily and record in the logbooks as per established protocol(19). Providers were encouraged to review retrospective glucose data using SMBG logbook with participants and use the data to adjust insulin and lifestyle recommendations for individualized management.

Both Arms

The study staff provided guidelines for routine diabetes management and education to participants in both arms. Follow-up visits for both arms occurred monthly on the usual clinic schedule. The CGM group had additional visits for new sensor insertion and data downloads. Study staff had phone calls with participants to review for any severe adverse events during the study. Participants in both groups received financial compensation for travel to the clinic for each study visit. All diabetes and testing materials were provided free to all participants.

Data collection and interviews

Quality of life and HbA1c were measured at baseline and the end of the study using the WHO Quality of Life questionnaire and a point of care HbA1c testing device, respectively. At each visit, logbooks for those in the usual care arm and Clarity reports for those in the CGM arm were reviewed. Five participants from each arm were interviewed by the study staff at baseline and endline to discuss their satisfaction with content, use, complexity, comfort, and challenges of CGM and glucose meter technology in their setting. Five providers were interviewed regarding their opinions on both technologies. The recruitment of study participants began in March 2022 and data collection was completed by July 2022.

Outcomes

While the primary aim of this study is to understand the feasibility of CGM in a low resource setting, it is also important to ensure that even if the technology is functional it does not have negative effects on clinical outcomes for users. For that reason we include two clinical

outcomes, HbA1c and time in range. Primary outcomes were split into implementation outcomes, defined using the Proctor (20) framework, and clinical outcomes.

Implementation outcomes

Fidelity

Fidelity is defined here using variables reflecting patients' adherence to the technology used (20). In the CGM arm, fidelity was defined by number of sensors worn, the percent of time sensors were worn (based on Clarity reports), and times that dose or lifestyle adjustments were made. In the usual care arm, fidelity was defined as the percent of expected blood glucose readings logged, the percent of participants who brought logbooks to the clinic during the study period, percent of expected times blood glucose test was performed, the number of times insulin adjustments were made, and how often lifestyle adjustments were suggested.

Appropriateness

Appropriateness was defined as the perceived fit and relevance or compatibility of CGM(20). This was based on sensor problems, reporting of technological issues, and qualitative interviews.

Clinical outcomes

Change in HbA1c

Change in Hba1c was measured as the change from baseline to endline measured using PTS diagnostics A1CNow+ point of care test kits. Due to lower than expected HbA1c measurements, we also included a comparison of endline HbA1c results and the 90-day estimated average glucose values calculated using Clarity reports of patients in the CGM arm of the study.

Severe adverse events

Severe adverse events were measured from patient self-reports, CGM or home glucose meters, or clinician reports.

Secondary outcomes

Implementation outcomes

Acceptability was defined using Proctor's framework as the perception that CGM was agreeable, palatable, or satisfactory (20). This was measured through qualitative interviews with PLWT1D and providers.

Clinical outcomes

We were only able to measure TIR in the CGM arm, which was calculated using downloaded CGM data. We defined "in range" as blood glucose reading between 70 mg/dL and 180 mg/dL (21). "Very high" was defined as over 250 mg/dL, and "very low" as below 54 mg/dL. Because two participants only had fewer than five days of CGM readings each, we included a sensitivity analysis removing these participants' data.

The standard deviation in HbA1c was calculated using the overall HbA1c SD in the baseline point-of-care tests. Quality of life (QoL) was measured using the WHO-BREF both at baseline and at the end of the study. The WHO-BREF includes four domains: Physical health, psychological, social relationships, and environment. QoL was calculated both by individual domain and overall.

Statistical methods

Statistical analyses were conducted using R version 4.2.2, or Stata version 14. We did not conduct sample size calculations because we recruited all PLWT1D receiving care at two PIH-assisted hospitals where this study was being conducted. Rather, we calculated power to detect the difference in HbA1c with the number of patients who participated (29 in the CGM arm and 13 in the usual care arm). Given a pooled standard deviation of 2.05 and an alpha level of 0.05, we had 80% power to detect a 1.96 percentage point difference in HbA1c between the two study arms in a two-sample t-test. Initial power calculations relied on a larger number of expected participants (13). We conducted analysis as intention to treat.

HbA1c analysis

To test whether the change in HbA1c differed between the CGM and usual care arms, we used the linear regression model specified below, equivalent to longitudinal analysis of covariance, where HbA1c at follow-up ($HbA1c_{t1}$) is predicted by study arm (SA), HbA1c at baseline ($HbA1c_{t0}$), facility site (Site), age (Age), female gender (Fem), diagnosis year (DY), and body mass index (BMI), with an error term, ε, assumed normally distributed. The coefficient on study arm, $\boldsymbol{\beta_1}$, was the parameter of interest.

$$HbA1c_{t1} = \beta_0 + SA\boldsymbol{\beta_1} + HbA1c_{t0}\beta_2 + Site\beta_3 + Age\beta_4 + Fem\beta_5 + DY\beta_6 + BMI\beta_7 + \varepsilon$$

We report the point estimate and 95% confidence interval for this parameter estimate from the fully adjusted model above as well as a minimally adjusted model, only including the terms for study arm and baseline HbA1c.

To test the relatively low HbA1c levels we compared the difference between endline HbA1c results and the 90-day estimated average glucose values for participants in the CGM arm. Estimated average glucose (EAG) was calculated in the Clarity application. The standard formula of EAG (mg/dL) = 28.7 x A1c – 46.7 was used to convert EAG to estimated HbA1c (34). Paired t-test was used to compare the estimated HbA1c to the point-of-care HbA1c.

Quality of life analysis

To estimate the difference in the change in QoL between study arms, we used the same approach as for HbA1c. We conducted a regression for each of the four domains of the WHO-BREF as well as the overall score, reporting the point estimate and 95% confidence interval for the estimated difference in the change between the arms from the fully adjusted model, adjusting for the same variables as in the HbA1c analysis described above except for BMI.

Percent of time worn and time in range analyses

This CGM device measures glucose levels roughly every five minutes. We summarized the measurements in several ways. First, we calculated the proportion of expected observations that were missing values. We did this by dividing time into five-minute increments. If no observation was present for a period longer than 5.06 minutes, we considered each five-minute increment between the previous and subsequent observations as missing. Then, we

calculated the proportion of all observations that were missing. We calculated the proportion of non-missing observations within the desired blood glucose range (70 to 180 mg/dL) to estimate time in range, as well as the proportion that were very low (under 54 mg/dL), low (54 mg/dL to 69 mg/dL), high (181 mg/dL -250 mg/dL), and very high (over 250 mg/dL). We additionally calculated the mean and interquartile range of the non-missing observations.

The CGM sensors lasted 10 days, but many patients returned to the clinic every 14 days to obtain replacement sensors. Therefore, a substantial proportion of the missingness was related to timing of sensor replacement. We estimated this proportion by assuming that any missingness on the day of a sensor replacement (recorded by study clinicians) was related to the replacement, and any missingness contiguous with (i.e., no non-missing observations between) and prior to (including in previous days) that period of missingness was categorized as related to the sensor replacement. We then tabulated the proportion of missing observations related to sensor replacement. Not all individuals experienced long periods missing a sensor, as some felt comfortable replacing sensors at home and were given extra sensors by study staff.

Qualitative methods

We conducted a series of semi-structured interviews with 10 patients (five in each arm) at the beginning and end of the study. We also interviewed five providers (two nurses and three clinicians) who provided care to the patients during the study period. Trained members of the study team conducted all interviews. Provider interviews were conducted in English. Patient interviews were conducted in Chichewa, and translated by a bilingual researcher. All interviews were audio recorded and transcribed by a trained researcher. Interviews were coded in Dedoose and analyzed using a thematic framework using a-priori themes.

Deviations from protocol

We initially planned a two-day training for participants, with one day devoted to comprehensive T1D education. However, due to long distances needed to travel for participants and resulting missed school and work, two consecutive days was not feasible.

Instead, for two months before the start of the study, providers gave enhanced diabetes education to all participants. In the protocol outcomes, we had stated the percent of expected times CGM and SMBG information was used to inform lifestyle-adjusted interventions, and we were unable to determine the percent so we used number of times instead.

Patient and public involvement

PLWT1D were engaged throughout the study. Three of the outcomes of this research were feasibility, acceptability, and appropriateness, so much of the study involved gaining perspectives, experiences and views of the technology by PLWT1D. Two of the study coauthors (GF & AG) are living with T1D, and were involved throughout the design of the protocol, tools, training and implementation of the study.

RESULTS

Participants

There were 45 individuals with T1D meeting the inclusion criteria at the two eligible hospitals. When approached by phone, all agreed to be included and were randomized, 30 to the CGM arm and 15 to the UC arm. On the day of trial initiation, one from the CGM arm and two from the UC arm did not present and therefore did not participate. At the end of the study, one participant in the CGM arm and two from the UC arm were not present for their final evaluations and were considered lost to follow-up (Figure 1). The trial was initiated on April 11th 2022 in Lisungwi district hospital and April 14th 2022 in Upper Neno district hospital and ran for 90 days. Table 1 shows baseline characteristics of trial participants in both arms.

Table 1: Characteristics of participants at baseline

	Study arm		**All participants (N=42)**
	CGM (N=29)	*Usual care (N=13)*	
Location (% Upper Neno)	48.0	46.0	47.6
Age (years) (mean (range))	30.9 (8, 51)	29.6 (8,46)	30.5 (8,51)
Age (years) (median)	32	30	31
Sex (%)			

Female Male	48.0 52.0	38.0 62.0	45.2 54.8
Age at diagnosis (mean (SD)) Age of diagnosis (median)	25 (10.1) 26	26.3 (9.9) 26	25.4 (10.4) 26
Years since diagnosis (mean (SD)) Years since diagnosis (median)	6.2 (6.2)) 4	3.7(1.7) 4	5.4 (5.3) 4
BMI (mean (SD))	21.4 (3.6)	24.5 (5.6)	22.4 (4.6)
Baseline HbA1c (%) (mean (SD))	8.5 (2.2)	7.9 (2.1)	8.3 (2.1)
Baseline total daily insulin dose (units/day)	53.59	49.23	52.24

*CGM: Continuous Glucose monitoring, SD: Standard deviation

Primary Outcomes

Implementation outcomes

Fidelity

Major fidelity outcomes are seen in Table 2 and Figure 2. There was a higher rate of consultations in the CGM arm (mean 8.3) compared to the usual care arm (1.3). In the CGM arm, participants used a mean of 6.8 sensors over the study period, with a range of 2 to 9 sensors. The average participant had recordings taken by their sensors for 63.8% of the time (median: 65.5%, interquartile range: 49.9-75.6%). A sensitivity analysis done dropping two individuals with only two days of observation made little change to the result (average 63.5% median: 65.5% IQR 49.3-75.7%). As many participants were unable to change the sensor on their own and clinic days were only once a week, there was, on average, a four-day lag between one sensor ending and the next sensor being applied. We estimated the amount of each individual's missingness due to this four-day lag and found that, on average, 72.7% of the missingness was due to lags between sensor changes (median: 83.4%, interquartile range (IQR): 63.7%-92.6%)). Sensitivity analysis showed only minimal change to the result (mean 74.4%; median 83.4%, IQR: 65.1%-92.6%)). Among the time we did not classify as "missing due to sensor change" because of missingness adjacent to documented sensor changes, participants had sensor recordings an average of 87.0% of the time (sensitivity analysis 86.9%).

Table 2: Measures of fidelity in participants

	Study arm

	CGM (N=29)	*Usual care (N=13)*
Consultations attended (mean)	8.3	1.3
Individuals with insulin adjustments (n (%))	20.0 (69.0)	2.0 (15.0)
Insulin adjustments made (n)	35.0	2.0
Insulin adjustments per individual (mean)	1.2	0.2
Lifestyle change suggestions (n)	13.0	3.0
Lifestyle change suggestions per individual (mean)	0.4	0.2
CGM arm		
Sensors worn, mean (range)	6.8 (2,9)	
Percent of time worn, mean (SD)	63.8 (16.1)	
Usual care arm		
Consultations with logbook brought to clinic (%)	75.0	
Readings logged (%)	51.3	

*CGM: Continuous glucose monitoring, SD: standard deviation.

In the usual care arm, participants brought logbooks to consultations 75% of the time. However, readings in logbooks corresponded to glucose meters readings only 51.3% of the time.

Of the 29 individuals in the CGM arm, 20 (69%) had an insulin adjustment made, compared with only two individuals (15%) in the UC arm. There were a total of 35 insulin adjustments in the CGM arm, which came to an average of 1.2 per individual, compared to 0.2 per individual in the UC arm. There were roughly double the amount of suggested lifestyle changes in the CGM arm (0.4 per person) compared to the UC arm (0.2) (Table 2).

Appropriateness

Over the course of the trial, only one participant in the trial arm was able to change the sensors himself. Two others felt confident to physically change the sensor but were unable to enter the code, so they still needed to come into the clinic to change the sensor. Clinicians reported that after multiple CGM insertions, patients felt confident with the application process and were able to self-apply with guidance, however they were unable to correctly input the sensor codes. In total, there were 28 cases of sensor failure over the three-month trial period. During the first sensor use, three individuals complained of

discomfort but worked with providers to find a more comfortable way of wearing them. In the first month, three participants accidentally removed the sensors, but there were no reported cases after the first month. Rashes and skin irritation were not a commonly encountered complaint in the CGM arm. The hot weather caused a few participants difficulty with keeping the sensor attached. We overcame this using skin Tac adhesive and cut-out tape overpatches to secure the sensors in place and prevent removal. No sensor related bleeding or potential skin reaction around or under the sensor was observed. There were no reported problems with the solar chargers, and participants were able to use the solar chargers for light in their houses.

Clinical outcomes

After three months, we observed an increase of 0.2 percentage points in HbA1c in the usual care arm (N= 11 as follow-up HbA1cs missing for two participants) and a reduction of 1.2 percentage points in the CGM arm (N=28) compared to baseline. After adjusting for baseline HbA1c levels and other covariates, participation in CGM compared to usual care was associated with a 1.1 percentage point lower HbA1c; confidence intervals were compatible with a moderate to null reduction in the CGM arm relative to the usual care arm (95% CI: 2.4 percentage point reduction to 0.3 percentage point increase, Table 3). Throughout the study there were three hospitalizations in the CGM arm and none in the usual care arm. None of the hospitalizations were attributed to the intervention. One was due to a long-standing non-healing diabetic foot issue, one was due to low blood sugar due to the participant having no food, and one was due to high blood glucose levels.

Mean endline point-of-care HbA1c was 7.4% (95% CI 6.6%, 8.1%). Mean estimated HbA1c was significantly higher, at 10.1% (95% CI 9.3%, 10.8%) and mean difference of 2.7% (95% CI 2.2%, 3.2%; $p < 0.05$). Supplementary Figure 1 shows point-of-care HbA1c and estimated HbA1c for each participant in the CGM arm.

Secondary Outcomes

Overall, participants and providers found the CGM devices acceptable. The main reported complaints concerned the length of time that sensors lasted, and the alarms on the CGM

monitors, and some participants reported not liking the visual aspect of the sensor. We go further into qualitative outcomes in our companion piece(22).

The average percent TIR in recorded readings (not including missing data) was 30.6% (SD 16.1%) (Figure 2). Among the 27 CGM arm participants with more than one week of recorded data, the average TIR was 32.6% (SD 14.7%). Over the course of the study, there was an increase in the time in the range starting in week 6 (Supplementary Figure 2). The average time in range was 30.8% in week 1, and 38.7% in week 10. To examine whether this increase in TIR was due to drop off of non-compliant participants, we conducted a sensitivity analysis looking at only participants who we had data for at 10 weeks. Among the 20 participants with greater than 5% non-missing data in week 10, the average time in range in week 1 was 34.5%, and the average in week 10 was 37.5% (Supplementary Figure 2).

Pretrial, there was a standard deviation of 2.1 in HbA1c pooled across two arms, although baseline HbA1c was low overall compared to what is generally expected in this type of setting(23-25).

Table 3: Change in HbA1c at three months

	Arm		Mean difference (95% CI)	P- value
	CGM (N=28) Mean (SD)	**UC N=11 Mean (SD)**		
HbA1c at follow-up	7.4 (1.9)	7.9 (2.0)		
Crude change from baseline	-1.2 (1.9)	0.2 (2.7)	-1.38 (-2.92, 0.17)	0.08
Model 1			-0.88 (-2.15, 0.40)	0.17
Model 2			-1.07 (-2.39, 0.26)	0.11

Model 1 adjusted for baseline HbA1c only; Model 2 adjusted for baseline HbA1c, facility site, age, sex, diagnosis year, and BMI. Note: 28 of the original 29 were included from the CGM arm because 1 person did not have a follow-up HbA1c measurement, and 11 of 13 were included in the usual care arm because of missing follow-up measures.
CGM: Continuous Glucose monitoring, CI: Confidence interval, SD: standard deviation

Over the course of the study, QoL (N=28 in CGM and N=10 in UC) was assessed using WHO-BREF increased across all domains (Supplementary Table 1). Though unadjusted QoL increased slightly more in the UC arm (9.0) than the CGM arm (6.7), confidence intervals for

differences in the change in QoL between groups were large, and we did not find any strong evidence of differences.

DISCUSSION

Summary of main results

This is the first RCT to be carried out in a rural area of a LIC on the feasibility of CGM. While participants wore their sensors just under two-thirds of the time, much of the missingness (over 70% on average) was attributable to their inability to change their sensors. The most pervasive barrier to CGM use among patients was the reported limited digital literacy and confidence with the sensor application process, which required patients in the CGM arm to come more frequently into the clinic than the usual care arm. However, with time and multiple CGM insertions, patients felt confident with the application process and could self-apply under the guidance of the clinicians, but still needed help with numerically entering sensor codes to activate them. Skin rashes were not a notable complaint, although due to the hot weather there was some difficulty with sensor adhesion that was rectified by using skin Tac adhesive and cut-out tape overpatches to secure the sensors in place. After the first few weeks, participants tolerated the CGM well, and clinicians were far more likely to make dose adjustments in the CGM arm than the usual care arm. There was a trend towards greater reduction in HbA1C in the CGM arm than in the usual care arm. However, there were many more consultations in the CGM arm, so it is difficult to attribute the improvement to the CGM or the greater number of consultations. Given the four-day lag between sensor end and replacement, the reduction may have been greater without this lag. The intervention was deemed acceptable by participants with the greatest complaint being around sensor beeping.

Comparisons with other studies

This is the first RCT conducted in a rural setting in a LIC to assess the feasibility of CGM and its effect on clinical outcomes and quality of life among people living with T1D. To date, there are less than a handful of studies on CGM use in the African continent, none of which are randomized control trials. One of these studies evaluated the glycemic profile – glucose exposure, variability, stability, and risk of hypoglycemia – of people living with T1D and T2D

in South Africa, across 16 different clinics(26). In Uganda, Niwaha and colleagues conducted a study to assess the risk of hypoglycemia for people living with T2D being treated with sulphonylureas or insulin and did not include PLWT1D(27). While the study in South Africa mentioned that some sensors failed to record data, neither this study nor that of Niwaha looked specifically at fidelity, appropriateness, or acceptability. A short observational study by McClure Yauch and Velazquez (2020) was conducted at national referral hospitals in urban areas in Kenya and Uganda to assess feasibility of CGM use and the glycemic profile of children and young adults affected by T1D using CGM technology (28). They found the use of this technology was tolerated by patients and expressed hope for wider use in the future. This urban study reported an average HbA1c of 10.9% with a SD of 2.7 compared to our average baseline HbA1c of 8.3% and endline HbA1c of 7.5% with a SD of 2.1. Their TIR was 31% compared to the TIR in our study of over 37% by week 10 (32.6% across the whole study period among the 27 participants in the CGM arm with more a few days of data). All three of these studies used the Freestyle Libre Pro, and users were blinded to their glucose data and had CGM use of 14 days. In our study we used the Dexcom G6 CGM for 90 days, which provides real-time glucose data to the user and can be used to make treatment decisions. None of these studies examined any association between CGM use and QOL.

Comparison of endline point-of-care HbA1c to estimated HbA1c based on CGM values showed that point-of-care HbA1c may be overestimating glycemic control. A few theories for the discrepancy between HbA1c and mean blood glucose levels have been proposed, including the presence of hemoglobinopathies, individual variations in the lifespan of red blood cells, renal impairment, and nutritional deficiencies (e.g., iron-deficiency anemia, Kwashiorkor, Marasmus) (29,30). No hemoglobinapathies are present in this patient population. Additionally, numerous assays for point-of-care HbA1c testing have become available over the last decade of possibly varying quality. These findings reinforce that HbA1c alone may not be adequate to evaluate glycemic control in PLWT1D, adding to current literature highlighting the importance of availability for additional ways to evaluate glycemic control, such as SMBG or CGM.

Despite challenges participants experienced with changing sensors and data missingness, the amount of glucose data recorded from sensor readings in this study - 63.8% of the time (median: 65.5%, interquartile range: 49.9-75.6% sensitivity analysis is mean: 63.5%; median: 65.5%; IQR; 49.3-75.7%.) and 87% when excluding missingness due to lag in sensor change – is higher than data from sensor readings [mean of 51.14 days (60.9%) (*SD* = 20.86), range 20–81 days] in a 90-day pre- and posttest pre-experimental study with children, adolescents, and young adults with poorly controlled diabetes living in the U.S.(31). This underscores the importance, benefits, and potential for high impact of ensuring access for glucose monitoring devices for PLWT1D in low-resources settings.

Limitations

This was a feasibility trial with only 42 individuals, it was not powered for seeing differences between study arms in outcomes like HbA1c and QoL. Due to the inability of patients in the CGM arm to change their device sensor, many patients ended up seeing providers twice a month compared to once a month in the usual care arm, making it difficult to separate effects of technology versus the effect of the increased frequency of visits. Additionally, providers were excited about the new technology and may have paid greater attention to patients in the CGM arm. All participants in the study had a diagnosis of T1D, however, limited resources and a lack of pancreatic antibody and C-peptide testing may mean some patients were misdiagnosed. This study was conducted for three months. While this is far longer than other studies, reduction in HbA1c levels and behavior change can take longer than three months, so a longer study may have found greater effects. Conversely, we do not know what adherence would look like after three months.

Implications for future research and practice

Our study suggests that CGM is feasible, appropriate, and acceptable in rural Malawi, and may show greater effectiveness in lowering HbA1c than SMBG. We highlight the need to include practical digital literacy and numeracy training for patients when considering CGM as a viable clinical option in diabetes management in such settings, and future studies and practice should explore ways participants with low literacy can learn to change sensors independently. Newer models of CGM (Dexcom G7, Freestyle Libre 2 and Freestyle Libre 3)

do not require sensor codes to be inputted for activation, so may be better suited to this setting. As devices were donated by Dexcom, this study did not examine costs, but continued global advocacy is necessary to ensure equitable access to intermediate T1D care for PLWT1D in LICs. Other studies may examine if short periods of intensive CGM use are equally effective as a training tool for both patients and providers allowing a more granular assessment of glycemic control than previously possible with glucose meters. In contrast, other studies looking at longer lengths of time using CGM may be able to explore if this is a tool that can enhance PLWT1D's understanding of their condition, improve diabetes self-management, decrease adverse events and diabetes-related complications, advance providers' skills and knowledge, and assist with decision-making around insulin initiation for people living with type 2 diabetes. Further, examining if there is added benefit and cost effectiveness of real-time CGM compared to flash glucose monitoring and un-blinded CGM compared to blinded in this setting is warranted.

CONCLUSION

This is the first RCT conducted on CGM in a rural region of a LIC. Overall, this small feasibility study conducted in one Malawian district found CGM to be feasible and appropriate among PLWT1D and their health care providers. Inability of participants to change their own sensor is the biggest challenge, though could be addressed with use of newer sensor models. Although not statistically significant, the downward trend in HbA1c in study arm is promising and worth investigating over a longer period, especially in light of increased TIR from baseline to endline. The current model of care needs to be strengthened and TIR continues to be low — posing higher risk for acute and chronic complications among this population.

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CONTRIBUTIONS

Study and tool design: AJA, TR, FV, CT, GF, AM, EW, CK, GB, PP.

Training: AG, CT, GF

Data analysis: MMC, FV, AG, AJA, AT, LD

All authors contributed to the final manuscript

GB, TR, and AJA share senior authorship.

COMPETING INTERESTS

The authors have no competing interests.

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DATA AVAILABILITY STATEMENT

De-identified data are available upon reasonable request from the corresponding author (AJA) at aadler2@bwh.harvard.edu.

FIGURES LEGEND

Figure 1: Consort study flow diagram

Figure 2: Time in range for each participant with missing data included and not included

Figure 2 caption: Note: individuals 27 and 29 used CGM devices for less than one week.

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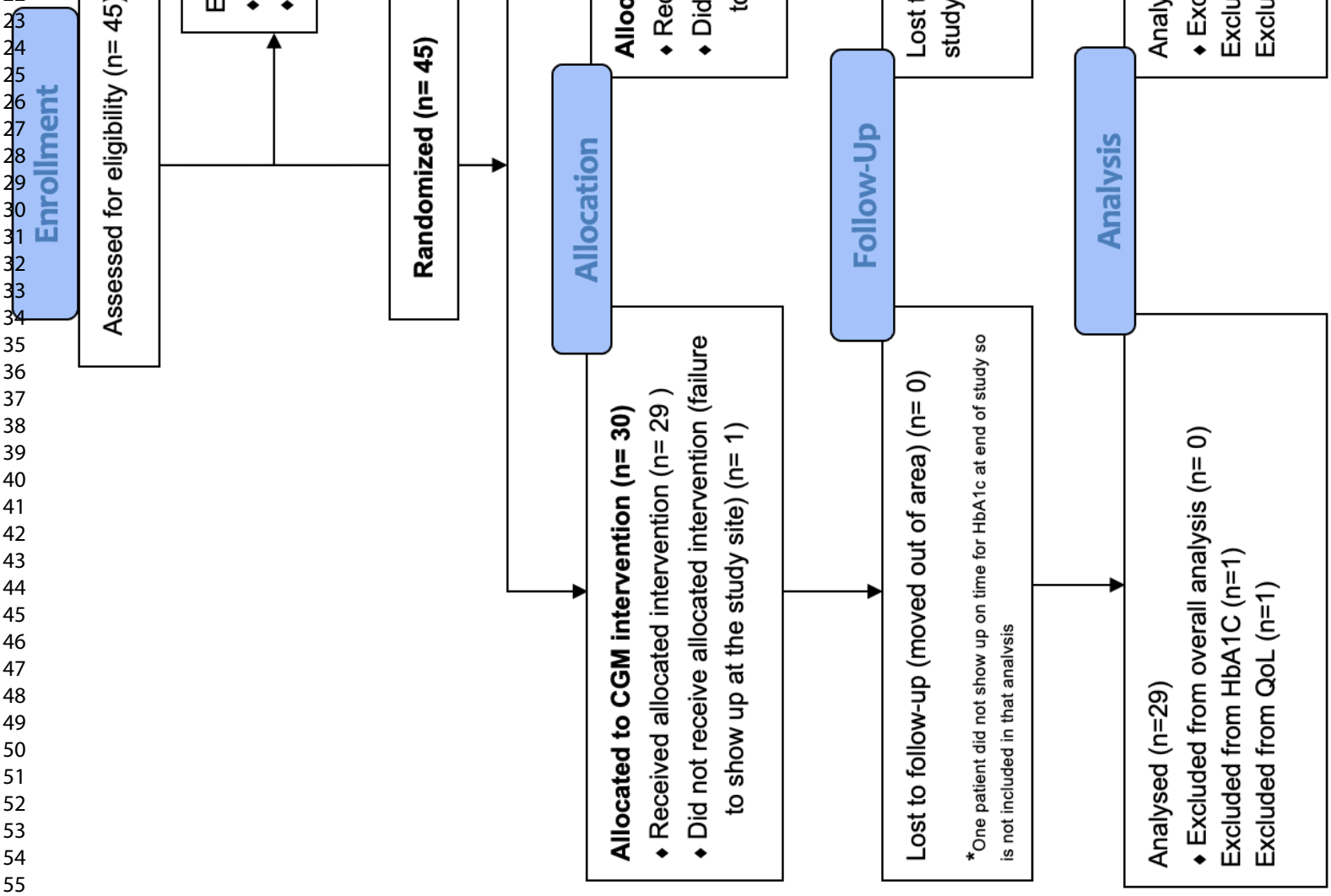
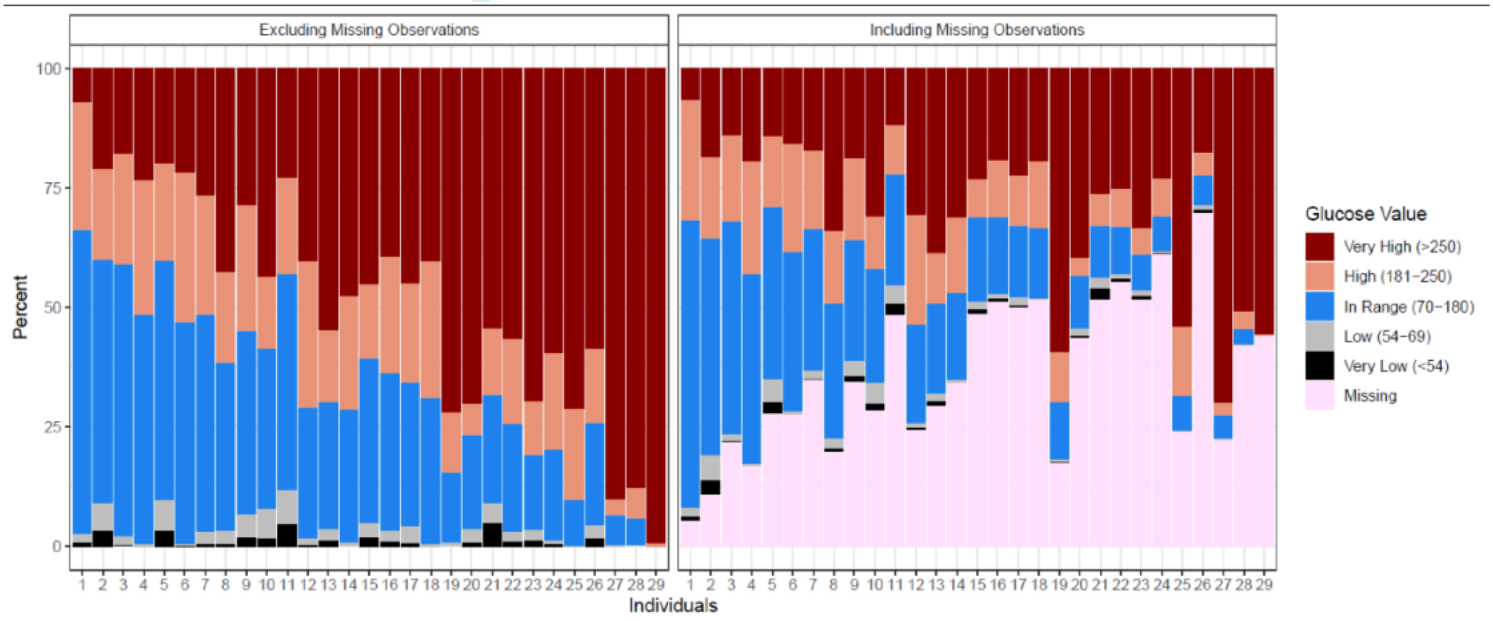

Enrollment
Assessed for eligibility (n= 45)
Excluded (n= 0)
◆ Not meeting inclusion criteria (n= 0)
◆ Declined to participate (n= 0)
Randomized (n= 45)
Allocation
Allocated to CGM intervention (n= 30)
◆ Received allocated intervention (n= 29)
◆ Did not receive allocated intervention (failure to show up at the study site) (n= 1)
Allocated to UC intervention (n=15)
◆ Received allocated intervention (n= 13)
◆ Did not receive allocated intervention (failure to show up at the study site) (n= 2)
Follow-Up
Lost to follow-up (moved out of area) (n= 0)
*One patient did not show up on time for HbA1c at end of study so is not included in that analysis
Lost to follow-up (Did not show up for end of study appointment) (n= 2)
Analysis
Analysed (n=29)
◆ Excluded from overall analysis (n= 0)
Excluded from HbA1C (n=1)
Excluded from QoL (n=1)
Analysed (n=11)
◆ Excluded from analysis (n= 0)
Excluded from HbA1c analysis (n=2)
Excluded from QoL analysis (n=3)


Excluding Missing Observations
Including Missing Observations
Percent
100
75
50
25
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Individuals
Glucose Value
Very High (>250)
High (181–250)
In Range (70–180)
Low (54–69)
Very Low (<54)
Missing

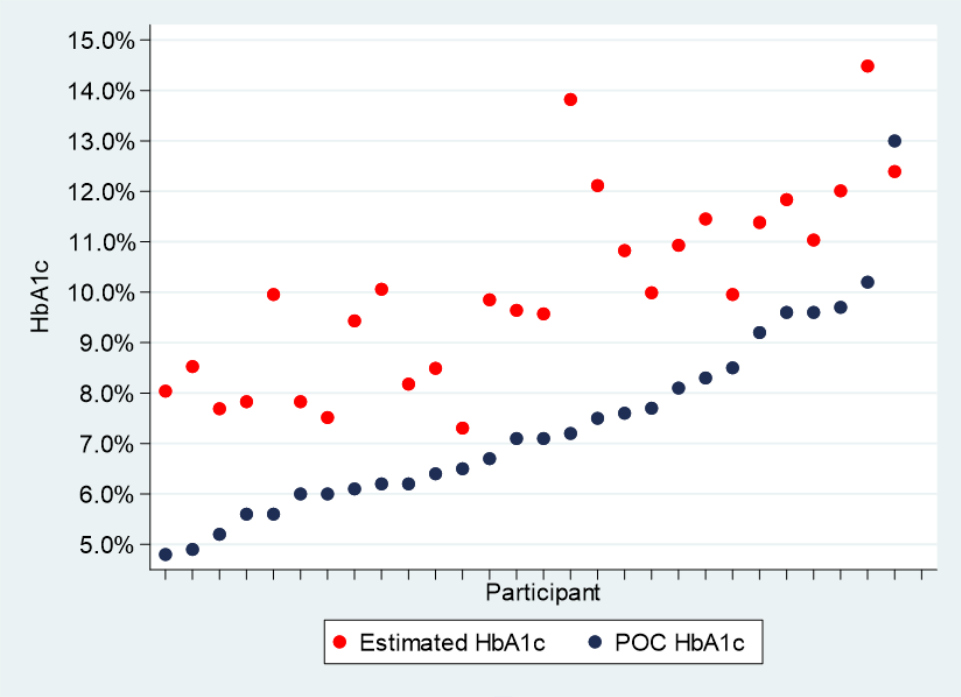
Supplementary Table 1: Quality of Life

	Crude			Adjusted Model		
	Pretest Mean (SD)	**Post test Mean (SD)**	**Difference**	**Coefficient**	**95% CI**	**P-value**
Domain 1: Physical health						
CGM	53.5 (13.1)	55.1 (14.6)	1.6	-4.32	-14.9, 6.2	0.41
UC	50.2 (18.4)	57.0 (9.1)	6.8			
Domain 2: Psychological						
CGM	53.2 (13.1)	57.6 (17.7)	4.4	0.36	-11.3, 12.6	0.95
UC	54.5 (15.5)	57.0 (18.0)	2.5			
Domain 3: Social relationships						
CGM	46.0 (17.9)	58.5 (23.3)	12.5	-8.94	-25.5, 7.6	0.28
UC	47.3 (29.9)	67.5 (20.5)	20.2			
Domain 4: Environment						
CGM	47.4 (16.3)	55.5 (17.1)	8.2	-0.84	-11.9, 10.2	0.88
UC	52.6 (18.7)	58.9 (21.2)	6.3			
Overall						
CGM	50.0 (12.5)	56.7 (15.6)	6.7	-3.75	-13.7, 6.2	0.45
UC	51.2 (16.7)	60.1 (14.7)	9.0			

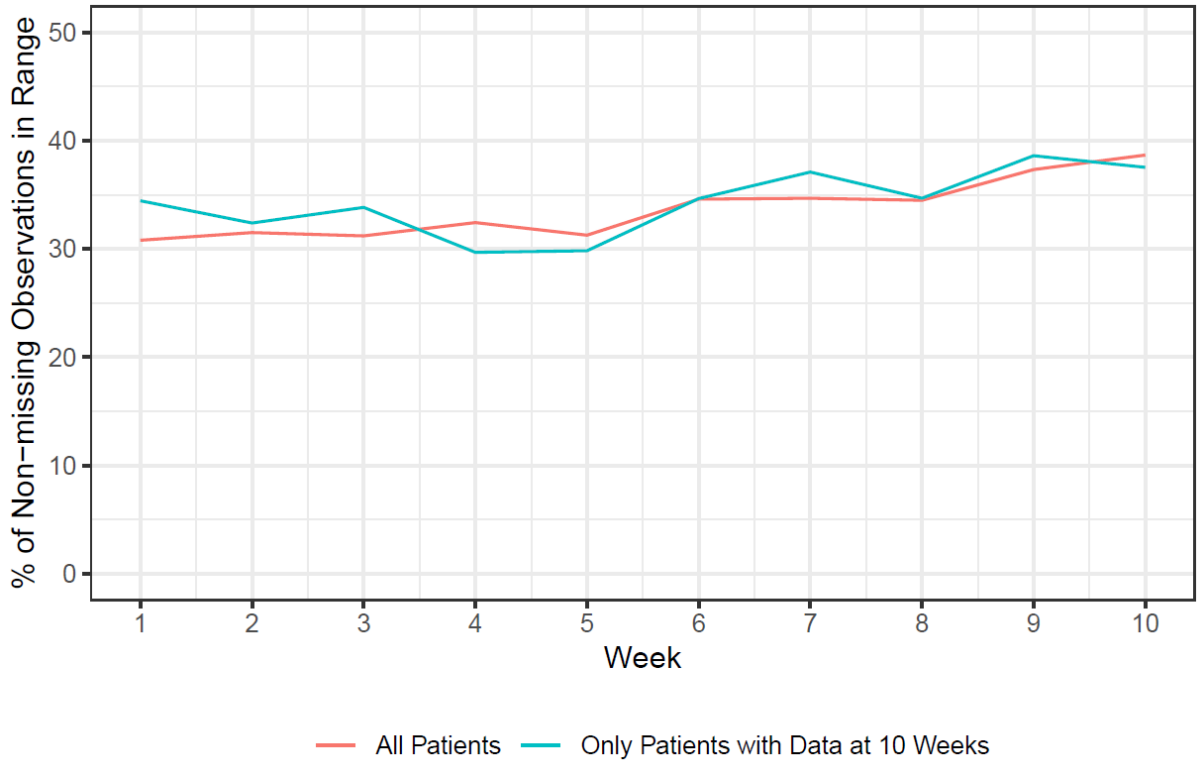
Note: There were 28 participants in the CGM arm and 10 in the usual care arm (1 and 3 of the original participants with no follow-up data in the respective arms). Coefficient, 95% CI, and p-value reported from longitudinal analysis of covariance, adjusted for baseline quality of life score, facility site, age, gender, and diagnosis year.

CGM: Continuous Glucose monitoring, CI: Confidence interval, SD: standard deviation

Supplementary Figure 1: For each participant, POC HbA1c compared to HbA1c estimated by 90-day average glucose from CGM wear



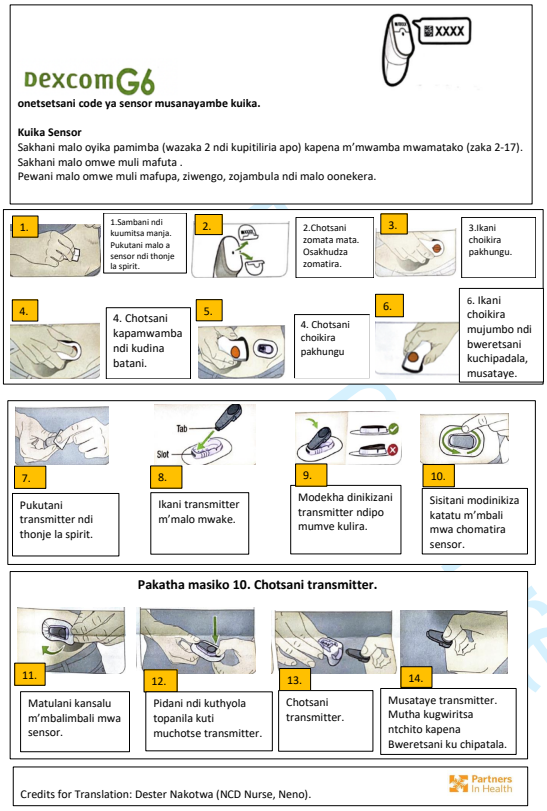
Supplementary Figure 2: Average time in range over course of ten weeks for participants with data at ten weeks



Appendices

Appendix A

Dexcom patient handout (English and Chichewa versions used during the study)



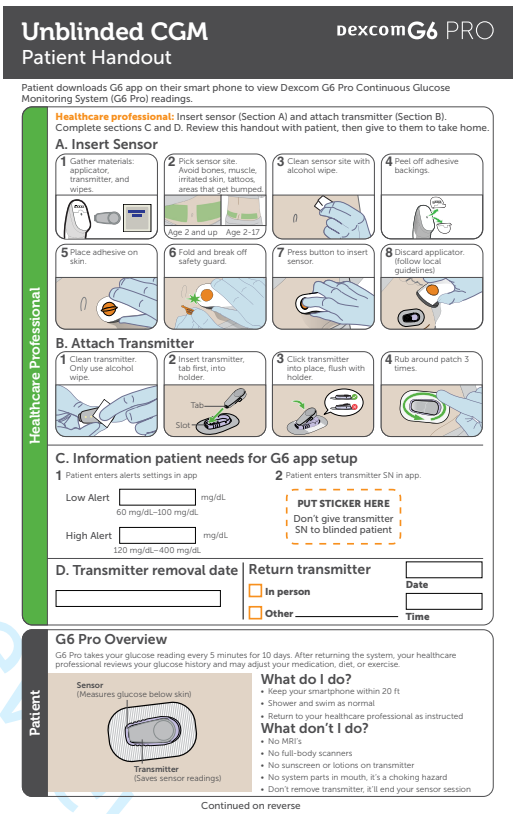


Table A : Training of participants performed in both arms and guidelines for clinicians

Participant Training at Baseline (For both groups): One session of general diabetes education and management

- Glucose targets
- Insulin dosing techniques and principles
  - Take before, not after each meal
  - Do not skip doses
- Basics of insulin therapy and meal planning
- Understanding signs and strategies for managing hypoglycemia and hyperglycemia
- Understanding sick day management.
- Understanding food insecurity and insulin therapy.

Clinician Guidelines:

- Providers were encouraged to review retrospective glucose data using SMBG logbook and CGM Clarity reports with participants and use the data to adjust insulin for individualized management.
- Make lifestyle and medication/insulin recommendations ***per usual practice***
- For CGM Group—CGM diabetes management guidelines

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of study as randomised pilot or feasibility trial	1
Authors *	Contact details for the corresponding author	31
Trial design	Description of pilot trial design (eg, parallel, cluster)	50
Methods		
Participants	Eligibility criteria for participants and the settings where the pilot trial was conducted	152-179
Interventions	Interventions intended for each group	208-237
Objective	Specific objectives of the pilot trial	141-146
Outcome	Prespecified assessment or measurement to address the pilot trial objectives**	252-307
Randomization	How participants were allocated to interventions	183-189
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	50
Results		
Numbers randomized	Number of participants screened and randomised to each group for the pilot trial objectives**	386-387
Recruitment	Trial status†	
Numbers analysed	Number of participants analysed in each group for the pilot objectives**	447,480-482,401
Outcome	Results for the pilot objectives, including any expressions of uncertainty**	401-496
Harms	Important adverse events or side effects	453
Conclusions	General interpretation of the results of pilot trial and their implications for the future definitive trial	588-598
Trial registration	Registration number for pilot trial and name of trial register	70
Funding	Source of funding for pilot trial	613-616

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

**this item is specific to conference abstracts*

***Space permitting, list all pilot trial objectives and give the results for each. Otherwise, report those that are a priori agreed as the most important to the decision to proceed with the future definitive RCT.*

†For conference abstracts.

BMJ Open

Randomized control trial for the feasibility of continuous glucose monitoring in patients with type 1 diabetes at two district hospitals in Neno, Malawi.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-075554.R2
Article Type:	Original research
Date Submitted by the Author:	05-Mar-2024
Complete List of Authors:	Gomber, Apoorva; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity Valeta, Francis; Partners in Health Coates, Matthew M.; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity Trujillo, Celina; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity; Partners In Health Ferrari, Gina; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity; Partners In Health Boti, Medson; Partners in Health Kumwenda, Kenwood; Partners in Health Mailosi, Bright ; Partners in Health Nakotwa, Dester; Partners in Health Drown, Laura ; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity Wroe, Emily B.; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity ; Partners In Health Thapa, Ada; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity Mithi, Victor; Partners In Health Matanje, Beatrice ; Partners In Health Msekandiana, Amos; Baylor College of Medicine; Kamuzu Central Hospital Park, Paul H; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity Kachimanga, Chiyembekezo; Partners In Health Bukhman, Gene; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity ; Partners In Health Ruderman, Todd; Partners in Health Adler, Alma; Brigham and Women's Hospital, Center for Integration Science, Division of Global Health Equity
Primary Subject Heading:	Global health
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES &

	ENDOCRINOLOGY, International health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Randomized control trial for the feasibility of continuous glucose monitoring in patients with type 1 diabetes at two district hospitals in Neno, Malawi.

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ABSTRACT

Objectives: To assess the feasibility and change in clinical outcomes associated with Continuous Glucose Monitoring (CGM) use among a rural population in Malawi living with type 1 diabetes **Design:** a 2:1 open randomized controlled feasibility trial
Setting: Two Partners In Health-supported Ministry of Health-run first level district hospitals in Neno, Malawi
Participants: 45 people living with type 1 diabetes
Interventions: Participants were randomly assigned to Dexcom G6 CGM (n=30) use or usual care (UC) (n=15) consisting of Safe-Accu glucose monitors and strips. Both arms received diabetes education.
Outcomes: Primary outcomes included fidelity, appropriateness, and severe adverse events. Secondary outcomes included change in HbA1c, acceptability, time in range (CGM arm only) standard deviation of HbA1c, and quality of life.
Results: Participants tolerated CGM well but were unable to change their own sensors which resulted in increased clinic visits in the CGM arm. Despite the hot climate, skin rashes were uncommon but cut-out tape overpatches were needed to secure the sensors in place. Participants in the CGM arm had greater numbers of dose adjustments and lifestyle change suggestions than those in the UC arm. Participants in the CGM arm wore their CGM on average 63.8% of the time. Participants in the UC arm brought logbooks to clinic 75% of the time. There were three hospitalizations all in the CGM arm, but none were related to the intervention.
Conclusions: This is the first RCT conducted on CGM in a rural region of a low-income country (LIC). CGM was feasible and appropriate among PLWT1D and providers, but inability of participants to change their own sensors is a challenge.
Trial registration: Trial registration number PACTR202102832069874. This study was approved by National Health Sciences Research Committee of Malawi (IRB Number IR800003905) and the Mass General Brigham (IRB number 2019P003554). The protocol was previously published.

Strengths and limitations of this study:

1. Randomized controlled trial evaluating feasibility and acceptability of CGM in a rural, low-literacy population in a low-income country
2. Study participants were followed for a period of 90 days, allowing for longitudinal data on impact of CGM
3. Limited by small sample size

Keywords: Type 1 diabetes, Continuous glucose monitoring (CGM), Self-monitoring, technology, feasibility study, RCT, Low income countries.

INTRODUCTION

Type 1 diabetes (T1D) is a severe autoimmune condition which leads to hyperglycemia and a lifelong insulin dependency(1). People living with type 1 diabetes (PLWT1D) require uninterrupted access to insulin, tools for glucose monitoring, adequate and uninterrupted access to needles and syringes, and continuous access to education and healthcare services to reduce the risk of mortality, adverse events, and long-term complications. In low-income countries (LICs) and lower-middle-income countries (LMICs) access to affordable and high-quality care is limited. T1D incidence and mortality in these settings are likely underestimated as misdiagnosis and non-diagnosis are common(2-5). Without adequate care, the life expectancy of a child with newly diagnosed T1D in most LICs might be as short as one year(6, 7). Evidence suggests that currently, almost 9 million individuals are living with T1D, of which one-fifth (1,665,997 people) are in LICs and middle-income countries(8). In Malawi, 6,530 people were estimated to be living with T1D in 2022 (8). Given these current estimates, it is imperative to improve diabetes care in these settings with integrated care delivery, education, and training.

An intermediate level of care for T1D (defined as multiple daily injections of insulin, self-monitoring of blood glucose (SMBG) 2–4 times per day, consistent point-of-care hemoglobin A1c (HbA1c), complication screening, and a team approach to diabetes education and support) is an achievable goal for resource-limited settings that could decrease complication rates and premature mortality (9).

SMBG has improved clinical outcomes and quality of life for PLWT1D and was the gold standard of care following the Diabetes Control and Complications Trial (DCCT)(10). Novel technological advances for glucose monitoring are now available, requiring an interstitial patch and a reader for real-time continuous glucose monitoring (CGM) using Bluetooth technology. Products including Dexcom G6 (Dexcom, Inc., San Diego, CA, USA) have reduced the burden of finger sticks by providing interstitial glucose readings, trends, and alerts in real-time with a significant reduction in the frequency of severe hypoglycemic episodes(11).

CGM addresses many limitations related to HbA1c testing and SMBG. HbA1c gives only a point estimate of the mean of blood glucose control. SMBG gives some information on variability

but not a complete picture, and neither provide real-time alerts about hypo- or hyperglycemia. The uptake of CGM devices in many high-income countries (HICs) is gradually increasing, with good acceptability and clinical outcomes. A recent international consensus statement on the use of CGM technology concluded that CGM data should be used for therapeutic treatment decisions related to hypoglycemia and glucose variability (12).

Currently, no data exist on the feasibility and effect on clinical outcomes of CGM for PLWT1D in rural areas of LICs especially in areas without electricity, and having low literacy and numeracy. To address this lack of evidence, we conducted a randomized trial to evaluate the feasibility of CGM technology and change in clinical outcomes among PLWT1D with limited literacy receiving diabetes care at two district hospitals in rural Malawi. Here we report quantitative results. While the qualitative results are important to understanding the feasibility of CGM in this setting, we report them in a separate paper to provide greater opportunity for discussion of themes and quotes (13). This study is approved by National Health Sciences Research Committee of Malawi (IRB Number IR800003905) and the Mass General Brigham (IRB number 2019P003554). The protocol was previously published(14).

OBJECTIVES

The objectives of this study are to (1) assess the feasibility and appropriateness of CGM use among a rural population of PLWT1D and limited literacy in an LIC; (2) to determine if CGM use can have an effect on diabetes clinical outcomes among PLWT1D in rural regions of LICs and (3) determine the standard deviation of HbA1c across individuals at baseline to inform further studies.

METHODS

Study setting

The study was conducted at two rural Ministry of Health (MOH) supported first-level hospitals in Neno district, Malawi, with a population of about 138,000(15), primarily relying on subsistence agriculture. Neno District Hospital is in a mountainous region near the Mozambique border and Lisungwi Community Hospital is in the lower, drier area near the Shire River. Both hospitals are similar in protocol and resources and are overseen by the same district leadership. Since 2007, Partners In Health (PIH), a US-based non-government

organization known locally as Abwenzi Pa Za Umoyo (APZU), has partnered with MOH to improve healthcare and socioeconomic development in Neno District. In 2018, two advanced non-communicable disease (NCD) clinics providing high-quality care for complex NCDs, consistent with the Package of essential medicines for noncommunicable diseases-Plus (PEN-Plus) opened at Upper Neno and Lisungwi(16-18). Patients with T1D enrolled in this clinic receive care from mid-level providers with specialized non-communicable disease (NCD) training. All insulin, syringes, and tools for SMBG are provided free of charge to all patients at their routine monthly appointments. PLWT1D typically use human insulin, intermediate-acting (NPH) two times daily and fast- acting (regular) two to three times daily. Every household in Neno is visited by a community health worker (CHW) monthly for education and screening for multiple common conditions, enrolment into maternal and chronic care, and accompaniment to the clinic(19).

Study Participants

Eligibility criteria for this study included a clinical diagnosis of T1D in PLWT1D, in diabetes care for at least one year, and seeking care at either of the PIH-supported MOH hospitals. We did not exclude anyone based on age. Exclusion criteria included pregnancy, mental impairment, and the inability of the subject or care provider to use a CGM device. Figure 1 shows the flow diagram of the recruitment process.

Each participant was required to complete an informed consent/ assent (children <18 years of age) form on the day of the enrolment. Study staff were trained to assist patients with limited literacy with the consent process.

Design

Randomization

All 45 participants known to have T1D and seeking care at hospitals in Neno met the study criteria and were approached for willingness to participate in this study. All agreed and were randomly assigned via a random numbers table to either of the two arms: CGM (Dexcom G6, Dexcom, Inc.) arm and usual care arm (using blood glucose meter) in a 2:1 ratio. Study

investigators and personnel were masked to the randomization sequence which was created by a senior researcher.

Provider training

Clinical providers were required to complete one month of virtual training on routine diabetes care and understanding CGM in the management of diabetes performed by the study team (including two nurse practitioners and two clinical officers trained in T1D care). Then, providers completed a two-week in-person hands-on training where they were required to wear a CGM and learn how to use Clarity (Dexcom CGM software). Providers were trained to review data from CGM downloads and SMBG logbook data and make individualized dose adjustments, changes in alarm alerts on the CGM reader, and recommendations for lifestyle and insulin dosing as per usual practice. Clear protocols warranting medical attention were supplied to the providers, and any reported adverse events were immediately assessed and documented. Provider training focused on: glucose targets; goal of time in range (TIR), insulin dosing techniques and principles; basics of insulin therapy and meal planning; understanding signs and strategies for managing hypoglycemia and hyperglycemia; understanding sick day management; understanding food insecurity and insulin dose adjustments; and troubleshooting common problems with Dexcom devices.

Intervention

Participants in the CGM arm were provided with a transmitter, a receiver, and sensors (Dexcom G6) inserted under the skin using an applicator to wear real-time continuous glucose monitoring technology for three months. All CGM equipment was provided free by Dexcom. Each transmitter had a shelf life of 90 days and each sensor had a shelf life of 10 days after which a new sensor needs to be applied. Participants in the CGM arm were instructed to use CGM daily and were advised to either change the sensor on their own or follow up after ten days for new sensor insertion. Individualized clinical recommendations were made by their providers at each visit using standardized material developed for the study based on Dexcom training materials (Appendix A). Participants in the CGM arm received a Chichewa-language handout at the beginning of the study to educate them about the features of CGM and readings obtained from the reader.

Comparator

Participants in the usual care arm were asked to perform home blood glucose monitoring using Safe Accu glucose meters and test strips at least once daily and record in the logbooks as per established protocol(20). Providers were encouraged to review retrospective glucose data using SMBG logbook with participants and use the data to adjust insulin and lifestyle recommendations for individualized management.

Both Arms

The study staff provided guidelines for routine diabetes management and education to participants in both arms. Follow-up visits for both arms occurred monthly on the usual clinic schedule. The CGM group had additional visits for new sensor insertion and data downloads. Study staff had phone calls with participants to review for any severe adverse events during the study. Participants in both groups received financial compensation for travel to the clinic for each study visit. All diabetes and testing materials were provided free to all participants.

Data collection and interviews

Quality of life and HbA1c were measured at baseline and the end of the study using the WHO Quality of Life questionnaire and a point of care HbA1c testing device, respectively. At each visit, logbooks for those in the usual care arm and Clarity reports for those in the CGM arm were reviewed. Five participants from each arm were interviewed by the study staff at baseline and endline to discuss their satisfaction with content, use, complexity, comfort, and challenges of CGM and glucose meter technology in their setting. Five providers were interviewed regarding their opinions on both technologies. The recruitment of study participants began in March 2022 and data collection was completed by July 2022.

Outcomes

While the primary aim of this study is to understand the feasibility of CGM in a low resource setting, it is also important to ensure that even if the technology is functional it does not

have negative effects on clinical outcomes for users. For that reason we include two clinical outcomes, HbA1c and time in range. Primary outcomes were split into implementation outcomes, defined using the Proctor (21) framework, and clinical outcomes.

Implementation outcomes

Fidelity

Fidelity is defined here using variables reflecting patients' adherence to the technology used (21). In the CGM arm, fidelity was defined by number of sensors worn, the percent of time sensors were worn (based on Clarity reports), and times that dose or lifestyle adjustments were made. In the usual care arm, fidelity was defined as the percent of expected blood glucose readings logged, the percent of participants who brought logbooks to the clinic during the study period, percent of expected times blood glucose test was performed, the number of times insulin adjustments were made, and how often lifestyle adjustments were suggested.

Appropriateness

Appropriateness was defined as the perceived fit and relevance or compatibility of CGM(21). This was based on sensor problems, reporting of technological issues, and qualitative interviews.

Clinical outcomes

Severe adverse events

Severe adverse events were measured from patient self-reports, CGM or home glucose meters, or clinician reports.

Secondary outcomes

Implementation outcomes

Acceptability was defined using Proctor's framework as the perception that CGM was agreeable, palatable, or satisfactory (21). This was measured through qualitative interviews with PLWT1D and providers.

Clinical outcomes

We were only able to measure TIR in the CGM arm, which was calculated using downloaded CGM data. We defined "in range" as blood glucose reading between 70 mg/dL and 180 mg/dL (22). "Very high" was defined as over 250 mg/dL, and "very low" as below 54 mg/dL. Because two participants only had fewer than five days of CGM readings each, we included a sensitivity analysis removing these participants' data.

Change in HbA1c

Change in Hba1c was measured as the change from baseline to endline measured using PTS diagnostics A1CNow+ point of care test kits. Due to lower than expected HbA1c measurements, we also included a comparison of endline HbA1c results and the 90-day estimated average glucose values calculated using Clarity reports of patients in the CGM arm of the study.

The standard deviation in HbA1c was calculated using the overall HbA1c SD in the baseline point-of-care tests. Quality of life (QoL) was measured using the WHO-BREF both at baseline and at the end of the study. The WHO-BREF includes four domains: Physical health, psychological, social relationships, and environment. QoL was calculated both by individual domain and overall.

Statistical methods

Statistical analyses were conducted using R version 4.2.2, or Stata version 14. We did not conduct sample size calculations because we recruited all PLWT1D receiving care at two PIH-assisted hospitals where this study was being conducted. Rather, we calculated power to detect the difference in HbA1c with the number of patients who participated (29 in the CGM arm and 13 in the usual care arm). Given a pooled standard deviation of 2.05 and an alpha level of 0.05, we had 80% power to detect a 1.96 percentage point difference in HbA1c between the two study arms in a two-sample t-test. Initial power calculations relied on a larger number of expected participants (14). We conducted analysis as intention to treat.

HbA1c analysis

To test whether the change in HbA1c differed between the CGM and usual care arms, we used the linear regression model specified below, equivalent to longitudinal analysis of covariance, where HbA1c at follow-up ($HbA1c_{t1}$) is predicted by study arm (SA), HbA1c at baseline ($HbA1c_{t0}$), facility site (Site), age (Age), female gender (Fem), diagnosis year (DY), and body mass index (BMI), with an error term, ε, assumed normally distributed. The coefficient on study arm, $\boldsymbol{\beta_1}$, was the parameter of interest.

$$HbA1c_{t1} = \beta_0 + SA\boldsymbol{\beta_1} + HbA1c_{t0}\beta_2 + Site\beta_3 + Age\beta_4 + Fem\beta_5 + DY\beta_6 + BMI\beta_7 + \varepsilon$$

We report the point estimate and 95% confidence interval for this parameter estimate from the fully adjusted model above as well as a minimally adjusted model, only including the terms for study arm and baseline HbA1c.

To test the relatively low HbA1c levels we compared the difference between endline HbA1c results and the 90-day estimated average glucose values for participants in the CGM arm. Estimated average glucose (EAG) was calculated in the Clarity application. The standard formula of EAG (mg/dL) = 28.7 x A1c – 46.7 was used to convert EAG to estimated HbA1c (23). Paired t-test was used to compare the estimated HbA1c to the point-of-care HbA1c.

Quality of life analysis

To estimate the difference in the change in QoL between study arms, we used the same approach as for HbA1c. We conducted a regression for each of the four domains of the WHO-BREF as well as the overall score, reporting the point estimate and 95% confidence interval for the estimated difference in the change between the arms from the fully adjusted model, adjusting for the same variables as in the HbA1c analysis described above except for BMI.

Percent of time worn and time in range analyses

This CGM device measures glucose levels roughly every five minutes. We summarized the measurements in several ways. First, we calculated the proportion of expected observations that were missing values. We did this by dividing time into five-minute increments. If no

observation was present for a period longer than 5.06 minutes, we considered each five-minute increment between the previous and subsequent observations as missing. Then, we calculated the proportion of all observations that were missing. We calculated the proportion of non-missing observations within the desired blood glucose range (70 to 180 mg/dL) to estimate time in range, as well as the proportion that were very low (under 54 mg/dL), low (54 mg/dL to 69 mg/dL), high (181 mg/dL -250 mg/dL), and very high (over 250 mg/dL). We additionally calculated the mean and interquartile range of the non-missing observations.

The CGM sensors lasted 10 days, but many patients returned to the clinic every 14 days to obtain replacement sensors. Therefore, a substantial proportion of the missingness was related to timing of sensor replacement. We estimated this proportion by assuming that any missingness on the day of a sensor replacement (recorded by study clinicians) was related to the replacement, and any missingness contiguous with (i.e., no non-missing observations between) and prior to (including in previous days) that period of missingness was categorized as related to the sensor replacement. We then tabulated the proportion of missing observations related to sensor replacement. Not all individuals experienced long periods missing a sensor, as some felt comfortable replacing sensors at home and were given extra sensors by study staff.

Qualitative methods

We conducted a series of semi-structured interviews with 10 patients (five in each arm) at the beginning and end of the study. We also interviewed five providers (two nurses and three clinicians) who provided care to the patients during the study period. Trained members of the study team conducted all interviews. Provider interviews were conducted in English. Patient interviews were conducted in Chichewa, and translated by a bilingual researcher. All interviews were audio recorded and transcribed by a trained researcher. Interviews were coded in Dedoose and analyzed using a thematic framework using a-priori themes.

Deviations from protocol

We initially planned a two-day training for participants, with one day devoted to comprehensive T1D education. However, due to long distances needed to travel for participants and resulting missed school and work, two consecutive days was not feasible. Instead, for two months before the start of the study, providers gave enhanced diabetes education to all participants. In the protocol outcomes, we had stated the percent of expected times CGM and SMBG information was used to inform lifestyle-adjusted interventions, and we were unable to determine the percent so we used number of times instead. We had initially included change in HbA1c as a primary outcome, but due to lack of power we changed this to a secondary outcome.

Patient and public involvement

PLWT1D were engaged throughout the study. Three of the outcomes of this research were feasibility, acceptability, and appropriateness, so much of the study involved gaining perspectives, experiences and views of the technology by PLWT1D. Two of the study coauthors (GF & AG) are living with T1D, and were involved throughout the design of the protocol, tools, training and implementation of the study.

RESULTS

Participants

There were 45 individuals with T1D meeting the inclusion criteria at the two eligible hospitals. When approached by phone, all agreed to be included and were randomized, 30 to the CGM arm and 15 to the UC arm. On the day of trial initiation, one from the CGM arm and two from the UC arm did not present and therefore did not participate. At the end of the study, one participant in the CGM arm and two from the UC arm were not present for their final evaluations and were considered lost to follow-up (Figure 1). The trial was initiated on April 11th 2022 in Lisungwi district hospital and April 14th 2022 in Upper Neno district hospital and ran for 90 days. Table 1 shows baseline characteristics of trial participants in both arms.

Table 1: Characteristics of participants at baseline

	Study arm	All

	CGM (N=29)	*Usual care (N=13)*	**participants (N=42)**
Location (% Upper Neno)	48.0	46.0	47.6
Age (years) (mean (range))	30.9 (8, 51)	29.6 (8,46)	30.5 (8,51)
Age (years) (median)	32	30	31
Sex (%)			
Female	48.0	38.0	45.2
Male	52.0	62.0	54.8
Age at diagnosis (mean (SD))	25 (10.1)	26.3 (9.9)	25.4 (10.4)
Age of diagnosis (median)	26	26	26
Years since diagnosis (mean (SD))	6.2 (6.2))	3.7(1.7)	5.4 (5.3)
Years since diagnosis (median)	4	4	4
BMI (mean (SD))	21.4 (3.6)	24.5 (5.6)	22.4 (4.6)
Baseline HbA1c (%) (mean (SD))	8.5 (2.2)	7.9 (2.1)	8.3 (2.1)
Baseline total daily insulin dose (units/day)	53.59	49.23	52.24

*CGM: Continuous Glucose monitoring, SD: Standard deviation

Primary Outcomes

Implementation outcomes

Fidelity

Major fidelity outcomes are seen in Table 2 and Figure 2. There was a higher rate of consultations in the CGM arm (mean 8.3) compared to the usual care arm (1.3). In the CGM arm, participants used a mean of 6.8 sensors over the study period, with a range of 2 to 9 sensors. The average participant had recordings taken by their sensors for 63.8% of the time (median: 65.5%, interquartile range: 49.9-75.6%). A sensitivity analysis done dropping two individuals with only two days of observation made little change to the result (average 63.5% median: 65.5% IQR 49.3-75.7%). As many participants were unable to change the sensor on their own and clinic days were only once a week, there was, on average, a four-day lag between one sensor ending and the next sensor being applied. We estimated the amount of each individual's missingness due to this four-day lag and found that, on average, 72.7% of the missingness was due to lags between sensor changes (median: 83.4%, interquartile range (IQR): 63.7%-92.6%)). Sensitivity analysis showed only minimal change to the result (mean 74.4%; median 83.4%, IQR: 65.1%-92.6%)). Among the time we did not classify as "missing due to sensor change" because of missingness adjacent to documented

sensor changes, participants had sensor recordings an average of 87.0% of the time (sensitivity analysis 86.9%).

Table 2: Measures of fidelity in participants

	Study arm	
	CGM (N=29)	*Usual care (N=13)*
Consultations attended (mean)	8.3	1.3
Individuals with insulin adjustments (n (%))	20.0 (69.0)	2.0 (15.0)
Insulin adjustments made (n)	35.0	2.0
Insulin adjustments per individual (mean)	1.2	0.2
Lifestyle change suggestions (n)	13.0	3.0
Lifestyle change suggestions per individual (mean)	0.4	0.2
CGM arm		
Sensors worn, mean (range)	6.8 (2,9)	
Percent of time worn, mean (SD)	63.8 (16.1)	
Usual care arm		
Consultations with logbook brought to clinic (%)	75.0	
Readings logged (%)	51.3	

*CGM: Continuous glucose monitoring, SD: standard deviation.

In the usual care arm, participants brought logbooks to consultations 75% of the time. However, readings in logbooks corresponded to glucose meters readings only 51.3% of the time.

Of the 29 individuals in the CGM arm, 20 (69%) had an insulin adjustment made, compared with only two individuals (15%) in the UC arm. There were a total of 35 insulin adjustments in the CGM arm, which came to an average of 1.2 per individual, compared to 0.2 per individual in the UC arm. There were roughly double the amount of suggested lifestyle changes in the CGM arm (0.4 per person) compared to the UC arm (0.2) (Table 2).

Appropriateness

Over the course of the trial, only one participant in the trial arm was able to change the sensors himself. Two others felt confident to physically change the sensor but were unable to enter the code, so they still needed to come into the clinic to change the sensor.

Clinicians reported that after multiple CGM insertions, patients felt confident with the application process and were able to self-apply with guidance, however they were unable to correctly input the sensor codes. In total, there were 28 cases of sensor failure over the three-month trial period. During the first sensor use, three individuals complained of discomfort but worked with providers to find a more comfortable way of wearing them. In the first month, three participants accidentally removed the sensors, but there were no reported cases after the first month. Rashes and skin irritation were not a commonly encountered complaint in the CGM arm. The hot weather caused a few participants difficulty with keeping the sensor attached. We overcame this using skin Tac adhesive and cut-out tape overpatches to secure the sensors in place and prevent removal. No sensor related bleeding or potential skin reaction around or under the sensor was observed. There were no reported problems with the solar chargers, and participants were able to use the solar chargers for light in their houses.

Clinical outcomes

Throughout the study there were three hospitalizations in the CGM arm and none in the usual care arm. None of the hospitalizations were attributed to the intervention. One was due to a long-standing non-healing diabetic foot issue, one was due to low blood sugar due to the participant having no food, and one was due to high blood glucose levels.

Mean endline point-of-care HbA1c was 7.4% (95% CI 6.6%, 8.1%). Mean estimated HbA1c was significantly higher, at 10.1% (95% CI 9.3%, 10.8%) and mean difference of 2.7% (95% CI 2.2%, 3.2%; $p < 0.05$). Supplementary Figure 1 shows point-of-care HbA1c and estimated HbA1c for each participant in the CGM arm.

Secondary Outcomes

Overall, participants and providers found the CGM devices acceptable. The main reported complaints concerned the length of time that sensors lasted, and the alarms on the CGM monitors, and some participants reported not liking the visual aspect of the sensor. We go further into qualitative outcomes in our companion piece(13).

The average percent TIR in recorded readings (not including missing data) was 30.6% (SD 16.1%) (Figure 2). Among the 27 CGM arm participants with more than one week of recorded data, the average TIR was 32.6% (SD 14.7%). Over the course of the study, there was an increase in the time in the range starting in week 6 (Supplementary Figure 2). The average time in range was 30.8% in week 1, and 38.7% in week 10. To examine whether this increase in TIR was due to drop off of non-compliant participants, we conducted a sensitivity analysis looking at only participants who we had data for at 10 weeks. Among the 20 participants with greater than 5% non-missing data in week 10, the average time in range in week 1 was 34.5%, and the average in week 10 was 37.5% (Supplementary Figure 2).

After three months, we observed an increase of 0.2 percentage points in HbA1c in the usual care arm (N= 11 as follow-up HbA1cs missing for two participants) and a reduction of 1.2 percentage points in the CGM arm (N=28) compared to baseline. After adjusting for baseline HbA1c levels and other covariates, participation in CGM compared to usual care was associated with a 1.1 percentage point lower HbA1c; confidence intervals were compatible with a moderate to null reduction in the CGM arm relative to the usual care arm (95% CI: 2.4 percentage point reduction to 0.3 percentage point increase, Table 3).

Pretrial, there was a standard deviation of 2.1 in HbA1c pooled across two arms, although baseline HbA1c was low overall compared to what is generally expected in this type of setting(24-26).

Table 3: Change in HbA1c at three months

	Arm		Mean difference (95% CI)	P- value
	CGM (N=28) Mean (SD)	**UC (N=11) Mean (SD)**		
HbA1c at follow-up	7.4 (1.9)	7.9 (2.0)		
Crude change from baseline	-1.2 (1.9)	0.2 (2.7)	-1.38 (-2.92, 0.17)	0.08
Model 1			-0.88 (-2.15, 0.40)	0.17
Model 2			-1.07 (-2.39, 0.26)	0.11

Model 1 adjusted for baseline HbA1c only; Model 2 adjusted for baseline HbA1c, facility site, age, sex, diagnosis year, and BMI. Note: 28 of the original 29 were included from the CGM

arm because 1 person did not have a follow-up HbA1c measurement, and 11 of 13 were included in the usual care arm because of missing follow-up measures.
CGM: Continuous Glucose monitoring, CI: Confidence interval, SD: standard deviation

Over the course of the study, QoL (N=28 in CGM and N=10 in UC) was assessed using WHO-BREF increased across all domains (Supplementary Table 1). Though unadjusted QoL increased slightly more in the UC arm (9.0) than the CGM arm (6.7), confidence intervals for differences in the change in QoL between groups were large, and we did not find any strong evidence of differences.

DISCUSSION

Summary of main results

This is the first RCT to be carried out in a rural area of a LIC on the feasibility of CGM. While participants wore their sensors just under two-thirds of the time, much of the missingness (over 70% on average) was attributable to their inability to change their sensors. The most pervasive barrier to CGM use among patients was the reported limited digital literacy and confidence with the sensor application process, which required patients in the CGM arm to come more frequently into the clinic than the usual care arm. However, with time and multiple CGM insertions, patients felt confident with the application process and could self-apply under the guidance of the clinicians, but still needed help with numerically entering sensor codes to activate them. Skin rashes were not a notable complaint, although due to the hot weather there was some difficulty with sensor adhesion that was rectified by using skin Tac adhesive and cut-out tape overpatches to secure the sensors in place. After the first few weeks, participants tolerated the CGM well, and clinicians were far more likely to make dose adjustments in the CGM arm than the usual care arm. There was a trend towards greater reduction in HbA1C in the CGM arm than in the usual care arm. However, there were many more consultations in the CGM arm, so it is difficult to attribute the improvement to the CGM or the greater number of consultations. Given the four-day lag between sensor end and replacement, the reduction may have been greater without this lag. The intervention was deemed acceptable by participants with the greatest complaint being around sensor beeping.

Comparisons with other studies

This is the first RCT conducted in a rural setting in a LIC to assess the feasibility of CGM and its effect on clinical outcomes and quality of life among people living with T1D. To date, there are less than a handful of studies on CGM use in the African continent, none of which are randomized control trials. One of these studies evaluated the glycemic profile – glucose exposure, variability, stability, and risk of hypoglycemia – of people living with T1D and T2D in South Africa, across 16 different clinics(27). In Uganda, Niwaha and colleagues conducted a study to assess the risk of hypoglycemia for people living with T2D being treated with sulphonylureas or insulin and did not include PLWT1D(28). While the study in South Africa mentioned that some sensors failed to record data, neither this study nor that of Niwaha looked specifically at fidelity, appropriateness, or acceptability. A short observational study by McClure Yauch and Velazquez (2020) was conducted at national referral hospitals in urban areas in Kenya and Uganda to assess feasibility of CGM use and the glycemic profile of children and young adults affected by T1D using CGM technology (29). They found the use of this technology was tolerated by patients and expressed hope for wider use in the future. This urban study reported an average HbA1c of 10.9% with a SD of 2.7 compared to our average baseline HbA1c of 8.3% and endline HbA1c of 7.5% with a SD of 2.1. Their TIR was 31% compared to the TIR in our study of over 37% by week 10 (32.6% across the whole study period among the 27 participants in the CGM arm with more a few days of data). All three of these studies used the Freestyle Libre Pro, and users were blinded to their glucose data and had CGM use of 14 days. In our study we used the Dexcom G6 CGM for 90 days, which provides real-time glucose data to the user and can be used to make treatment decisions. None of these studies examined any association between CGM use and QOL.

Comparison of endline point-of-care HbA1c to estimated HbA1c based on CGM values showed that point-of-care HbA1c may be overestimating glycemic control. A few theories for the discrepancy between HbA1c and mean blood glucose levels have been proposed, including the presence of hemoglobinopathies, individual variations in the lifespan of red blood cells, renal impairment, and nutritional deficiencies (e.g., iron-deficiency anemia, Kwashiorkor, Marasmus) (30,31). No hemoglobinapathies are present in this patient population. Additionally, numerous assays for point-of-care HbA1c testing have become

available over the last decade of possibly varying quality. These findings reinforce that HbA1c alone may not be adequate to evaluate glycemic control in PLWT1D, adding to current literature highlighting the importance of availability for additional ways to evaluate glycemic control, such as SMBG or CGM.

Despite challenges participants experienced with changing sensors and data missingness, the amount of glucose data recorded from sensor readings in this study - 63.8% of the time (median: 65.5%, interquartile range: 49.9-75.6% sensitivity analysis is mean: 63.5%; median: 65.5%; IQR; 49.3-75.7%.) and 87% when excluding missingness due to lag in sensor change – is higher than data from sensor readings [mean of 51.14 days (60.9%) (*SD* = 20.86), range 20–81 days] in a 90-day pre- and posttest pre-experimental study with children, adolescents, and young adults with poorly controlled diabetes living in the U.S.(32). This underscores the importance, benefits, and potential for high impact of ensuring access for glucose monitoring devices for PLWT1D in low-resources settings.

Limitations

This was a feasibility trial with only 42 individuals, it was not powered for seeing differences between study arms in outcomes like HbA1c and QoL. Due to the inability of patients in the CGM arm to change their device sensor, many patients ended up seeing providers twice a month compared to once a month in the usual care arm, making it difficult to separate effects of technology versus the effect of the increased frequency of visits. Additionally, providers were excited about the new technology and may have paid greater attention to patients in the CGM arm. All participants in the study had a diagnosis of T1D, however, limited resources and a lack of pancreatic antibody and C-peptide testing may mean some patients were misdiagnosed. This study was conducted for three months. While this is far longer than other studies, reduction in HbA1c levels and behavior change can take longer than three months, so a longer study may have found greater effects. Conversely, we do not know what adherence would look like after three months.

Implications for future research and practice

Our study suggests that CGM is feasible, appropriate, and acceptable in rural Malawi, and may show greater effectiveness in lowering HbA1c than SMBG. We highlight the need to include practical digital literacy and numeracy training for patients when considering CGM as a viable clinical option in diabetes management in such settings, and future studies and practice should explore ways participants with low literacy can learn to change sensors independently. Newer models of CGM (Dexcom G7, Freestyle Libre 2 and Freestyle Libre 3) do not require sensor codes to be inputted for activation, so may be better suited to this setting. As devices were donated by Dexcom, this study did not examine costs, but continued global advocacy is necessary to ensure equitable access to intermediate T1D care for PLWT1D in LICs. Other studies may examine if short periods of intensive CGM use are equally effective as a training tool for both patients and providers allowing a more granular assessment of glycemic control than previously possible with glucose meters. In contrast, other studies looking at longer lengths of time using CGM may be able to explore if this is a tool that can enhance PLWT1D's understanding of their condition, improve diabetes self-management, decrease adverse events and diabetes-related complications, advance providers' skills and knowledge, and assist with decision-making around insulin initiation for people living with type 2 diabetes. Further, examining if there is added benefit and cost effectiveness of real-time CGM compared to flash glucose monitoring and un-blinded CGM compared to blinded in this setting is warranted.

CONCLUSION

This is the first RCT conducted on CGM in a rural region of a LIC. Overall, this small feasibility study conducted in one Malawian district found CGM to be feasible and appropriate among PLWT1D and their health care providers. Inability of participants to change their own sensor is the biggest challenge, though could be addressed with use of newer sensor models. Although not statistically significant, the downward trend in HbA1c in study arm is promising and worth investigating over a longer period, especially in light of increased TIR from baseline to endline. The current model of care needs to be strengthened and TIR continues to be low — posing higher risk for acute and chronic complications among this population.

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CONTRIBUTIONS

Study and tool design: AJA, TR, FV, CT, GF, AM, EW, CK, GB, PP.

Training: AG, CT, GF

Data analysis: MMC, FV, AG, AJA, AT, LD

All authors contributed to the final manuscript

GB, TR, and AJA share senior authorship.

COMPETING INTERESTS

The authors have no competing interests.

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DATA AVAILABILITY STATEMENT

De-identified data are available upon reasonable request from the corresponding author (AJA) at aadler2@bwh.harvard.edu.

FIGURES LEGEND

Figure 1: Consort study flow diagram

Figure 2: Time in range for each participant with missing data included and not included

Figure 2 caption: Note: individuals 27 and 29 used CGM devices for less than one week.

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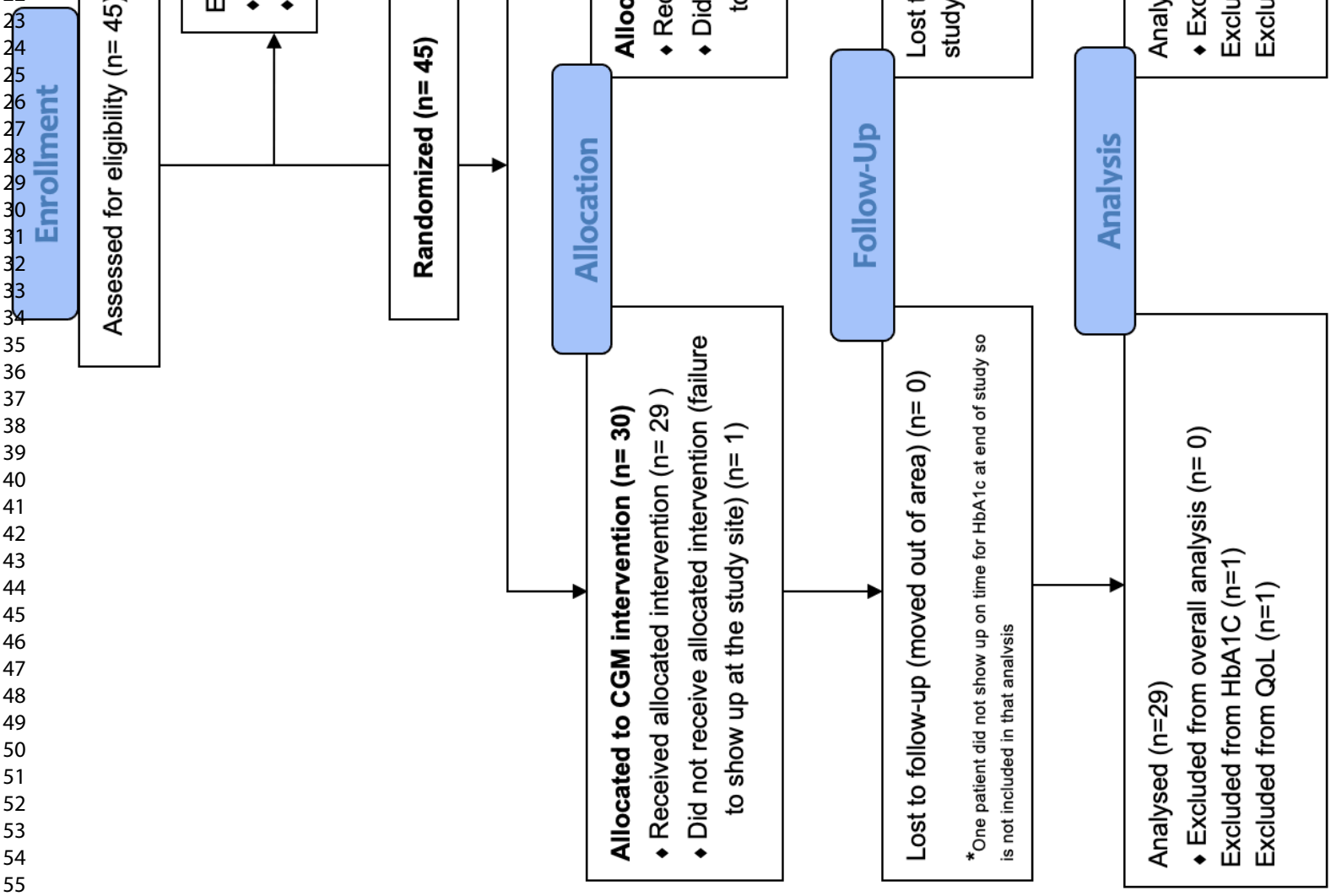
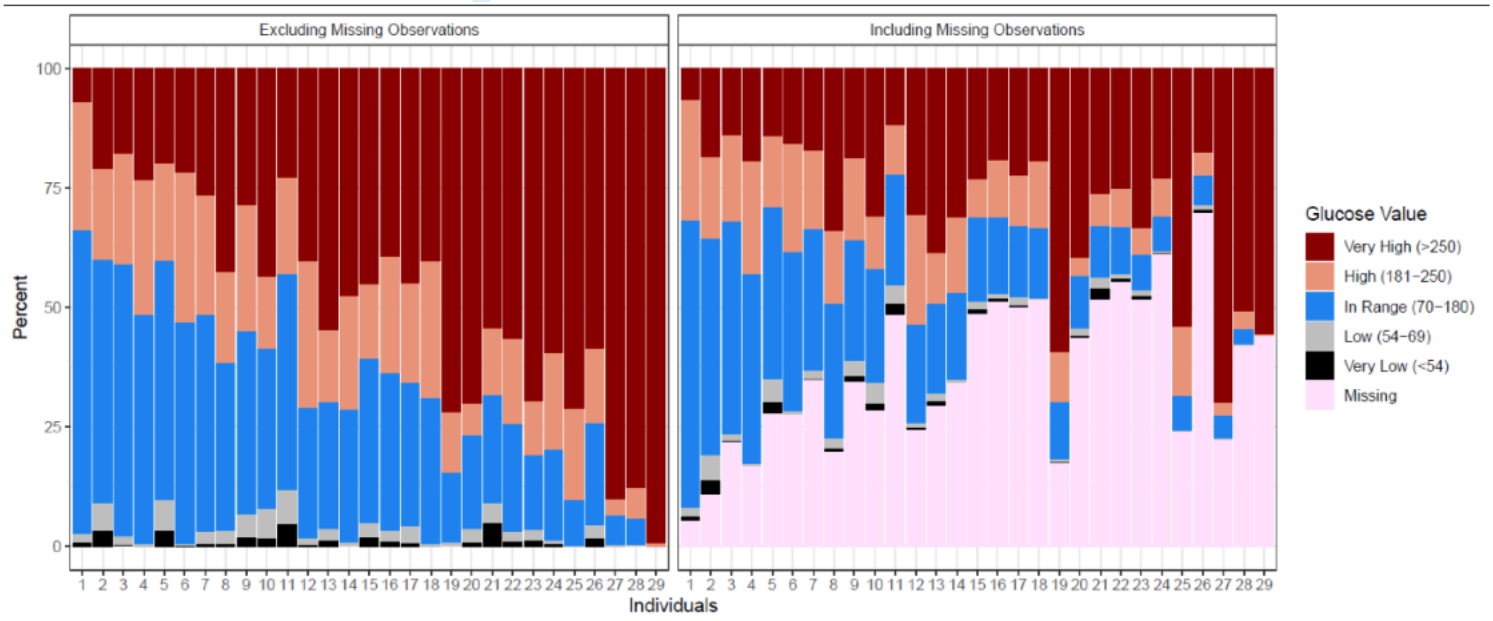

Enrollment
Assessed for eligibility (n= 45)
Excluded (n= 0)
◆ Not meeting inclusion criteria (n= 0)
◆ Declined to participate (n= 0)
Randomized (n= 45)
Allocation
Allocated to CGM intervention (n= 30)
◆ Received allocated intervention (n= 29)
◆ Did not receive allocated intervention (failure to show up at the study site) (n= 1)
Allocated to UC intervention (n=15)
◆ Received allocated intervention (n= 13)
◆ Did not receive allocated intervention (failure to show up at the study site) (n= 2)
Follow-Up
Lost to follow-up (moved out of area) (n= 0)
*One patient did not show up on time for HbA1c at end of study so is not included in that analysis
Lost to follow-up (Did not show up for end of study appointment) (n= 2)
Analysis
Analysed (n=29)
◆ Excluded from overall analysis (n= 0)
Excluded from HbA1C (n=1)
Excluded from QoL (n=1)
Analysed (n=11)
◆ Excluded from analysis (n= 0)
Excluded from HbA1c analysis (n=2)
Excluded from QoL analysis (n=3)


Excluding Missing Observations
Including Missing Observations
Percent
100
75
50
25
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Individuals
Glucose Value
Very High (>250)
High (181–250)
In Range (70–180)
Low (54–69)
Very Low (<54)
Missing

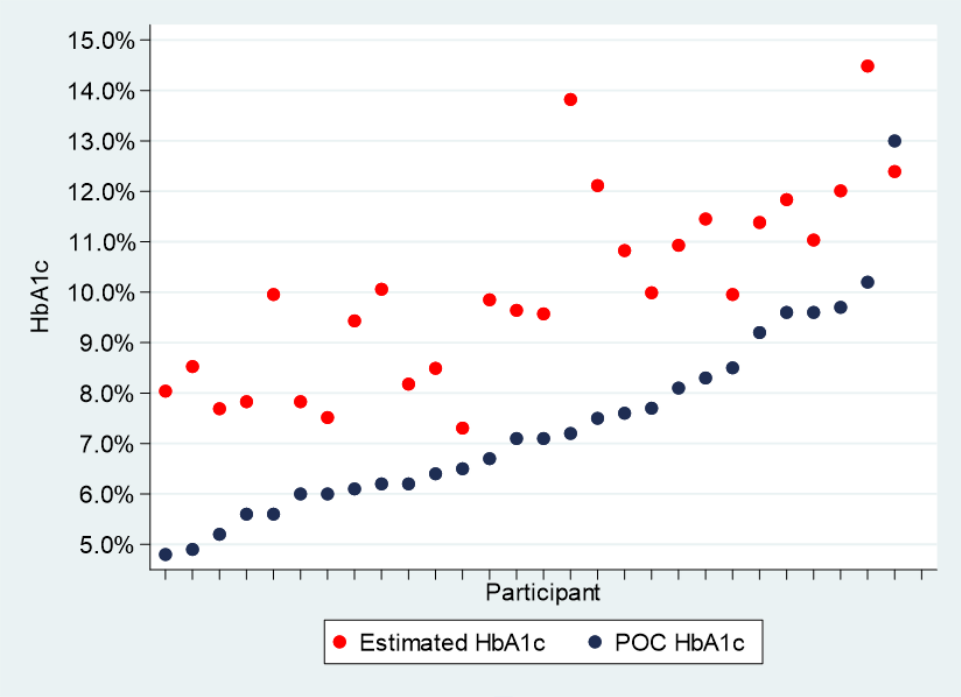
Supplementary Table 1: Quality of Life

	Crude			Adjusted Model		
	Pretest Mean (SD)	**Post test Mean (SD)**	**Difference**	**Coefficient**	**95% CI**	**P-value**
Domain 1: Physical health						
CGM	53.5 (13.1)	55.1 (14.6)	1.6	-4.32	-14.9, 6.2	0.41
UC	50.2 (18.4)	57.0 (9.1)	6.8			
Domain 2: Psychological						
CGM	53.2 (13.1)	57.6 (17.7)	4.4	0.36	-11.3, 12.6	0.95
UC	54.5 (15.5)	57.0 (18.0)	2.5			
Domain 3: Social relationships						
CGM	46.0 (17.9)	58.5 (23.3)	12.5	-8.94	-25.5, 7.6	0.28
UC	47.3 (29.9)	67.5 (20.5)	20.2			
Domain 4: Environment						
CGM	47.4 (16.3)	55.5 (17.1)	8.2	-0.84	-11.9, 10.2	0.88
UC	52.6 (18.7)	58.9 (21.2)	6.3			
Overall						
CGM	50.0 (12.5)	56.7 (15.6)	6.7	-3.75	-13.7, 6.2	0.45
UC	51.2 (16.7)	60.1 (14.7)	9.0			

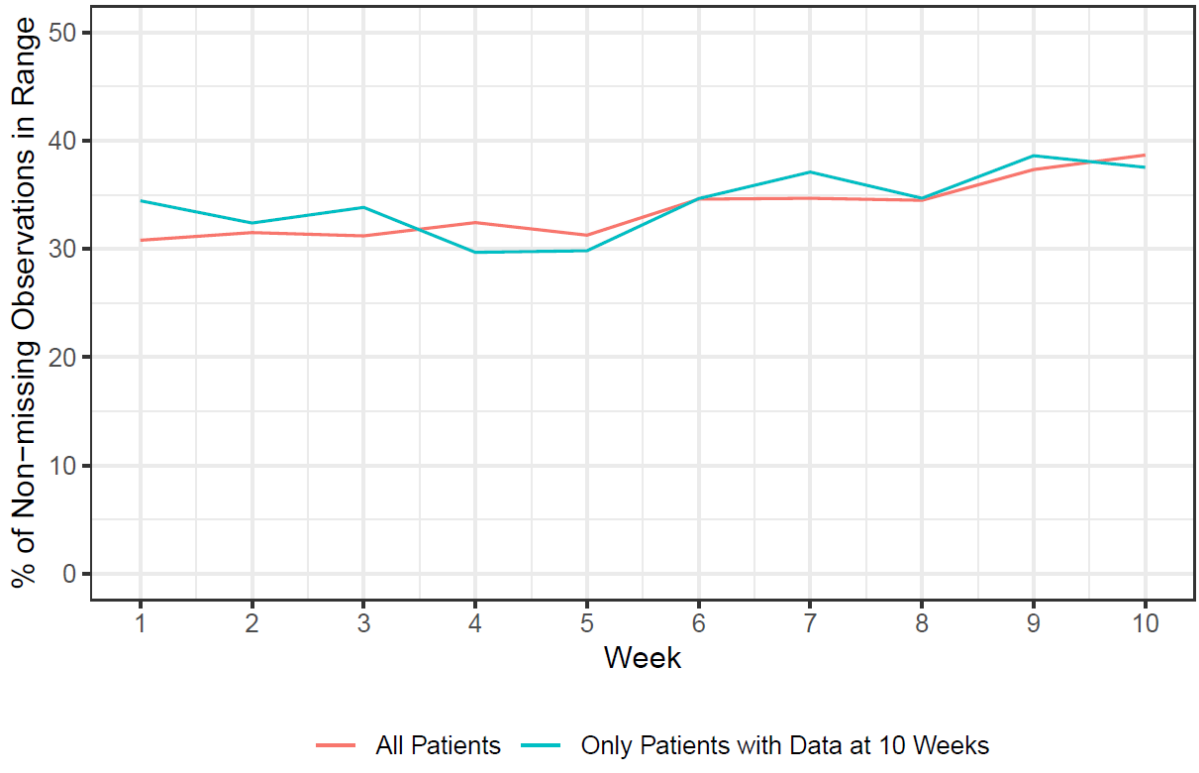
Note: There were 28 participants in the CGM arm and 10 in the usual care arm (1 and 3 of the original participants with no follow-up data in the respective arms). Coefficient, 95% CI, and p-value reported from longitudinal analysis of covariance, adjusted for baseline quality of life score, facility site, age, gender, and diagnosis year.

CGM: Continuous Glucose monitoring, CI: Confidence interval, SD: standard deviation

Supplementary Figure 1: For each participant, POC HbA1c compared to HbA1c estimated by 90-day average glucose from CGM wear



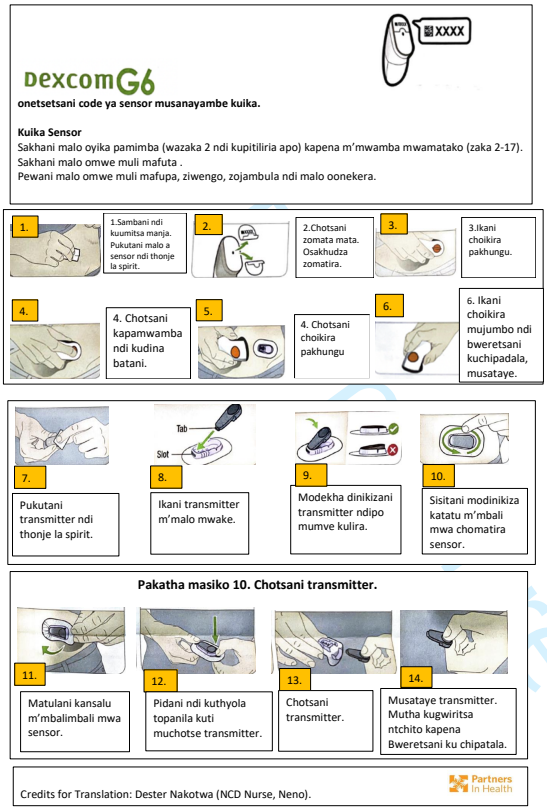
Supplementary Figure 2: Average time in range over course of ten weeks for participants with data at ten weeks



Appendices

Appendix A

Dexcom patient handout (English and Chichewa versions used during the study)



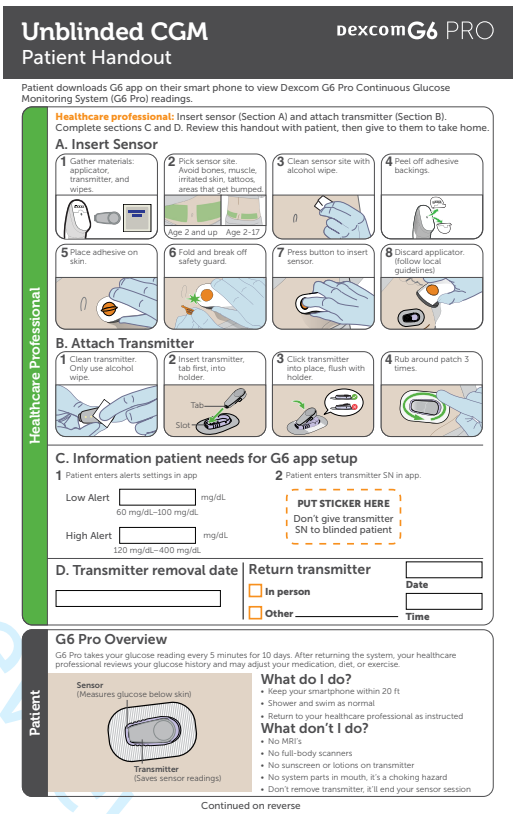


Table A : Training of participants performed in both arms and guidelines for clinicians

Participant Training at Baseline (For both groups): One session of general diabetes education and management

- Glucose targets
- Insulin dosing techniques and principles
  - Take before, not after each meal
  - Do not skip doses
- Basics of insulin therapy and meal planning
- Understanding signs and strategies for managing hypoglycemia and hyperglycemia
- Understanding sick day management.
- Understanding food insecurity and insulin therapy.

Clinician Guidelines:

- Providers were encouraged to review retrospective glucose data using SMBG logbook and CGM Clarity reports with participants and use the data to adjust insulin for individualized management.
- Make lifestyle and medication/insulin recommendations ***per usual practice***
- For CGM Group—CGM diabetes management guidelines

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of study as randomised pilot or feasibility trial	1
Authors *	Contact details for the corresponding author	31
Trial design	Description of pilot trial design (eg, parallel, cluster)	50
Methods		
Participants	Eligibility criteria for participants and the settings where the pilot trial was conducted	152-179
Interventions	Interventions intended for each group	208-237
Objective	Specific objectives of the pilot trial	141-146
Outcome	Prespecified assessment or measurement to address the pilot trial objectives**	252-307
Randomization	How participants were allocated to interventions	183-189
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	50
Results		
Numbers randomized	Number of participants screened and randomised to each group for the pilot trial objectives**	386-387
Recruitment	Trial status†	
Numbers analysed	Number of participants analysed in each group for the pilot objectives**	447,480-482,401
Outcome	Results for the pilot objectives, including any expressions of uncertainty**	401-496
Harms	Important adverse events or side effects	453
Conclusions	General interpretation of the results of pilot trial and their implications for the future definitive trial	588-598
Trial registration	Registration number for pilot trial and name of trial register	70
Funding	Source of funding for pilot trial	613-616

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

**this item is specific to conference abstracts*

***Space permitting, list all pilot trial objectives and give the results for each. Otherwise, report those that are a priori agreed as the most important to the decision to proceed with the future definitive RCT.*

†For conference abstracts.