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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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3 **1 Randomized control trial for the feasibility of continuous glucose monitoring in patients**
4 **2 with type 1 diabetes at two district hospitals in Neno, Malawi.**
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3 45 **ABSTRACT**
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6 47 **Objectives:** To assess the feasibility and clinical effectiveness of Continuous Glucose
7 48 Monitoring (CGM) use among a rural population in Malawi living with type 1 diabetes

8 49 **Design:** a 2:1 open randomized controlled feasibility trial

9 50 **Setting:** Two Partners In Health-supported Ministry of Health-run first level district hospitals
10 51 in Neno, Malawi

11 52 **Participants:** 45 people living with type 1 diabetes

12 53 **Interventions:** Participants were randomly assigned to Dexcom G6 CGM (n=30) use or usual
13 54 care (UC) (n=15) consisting of Safe-Accu glucose monitors and strips. Both arms received
14 55 diabetes education.

15 56 **Outcomes:** Primary outcomes included fidelity, appropriateness, change in HbA1c, and
16 57 severe adverse events. Secondary outcomes included acceptability, time in range (CGM arm
17 58 only) standard deviation of HbA1c, and quality of life.

18 59 **Results:** Participants tolerated CGM well but were unable to change their own sensors
19 60 which resulted in increased clinic visits in the CGM arm. Participants in the CGM arm had
20 61 greater numbers of dose adjustments and lifestyle change suggestions than those in the UC
21 62 arm. There was a trend towards reduction of HbA1c in the CGM arm (-1.1% 95%CI -2.4, 0.3).
22 63 Participants in the CGM arm wore their CGM on average 63.8% of the time. Participants in
23 64 the UC arm brought logbooks to clinic 75% of the time. There were three hospitalizations all
24 65 in the CGM arm, but none were related to the intervention.

25 66 **Conclusions:** This is the first RCT conducted on CGM in a rural region of a low-income
26 67 country (LIC). CGM was feasible and appropriate among PLWT1D and providers, but
27 68 inability of participants to change their own sensors is a challenge.

28 69 **Trial registration:** Trial registration number PACTR202102832069874. This study was
29 70 approved by National Health Sciences Research Committee of Malawi (IRB Number
30 71 IR800003905) and the Mass General Brigham (IRB number 2019P003554). The protocol was
31 72 previously published(1).
32 73

33 74 **Strengths and limitations of this study:**
34 75

- 35 76 1. The first RCT evaluating feasibility and acceptability of CGM in a rural, low-literacy
36 77 population in a low-income country
37 78 2. Study participants were followed for a period of 90 days, allowing for longitudinal data
38 79 on impact of CGM
39 80 3. Limited by small sample size
40 81

41 82
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43 84
44 85 **Keywords:** Type 1 diabetes, Continuous glucose monitoring (CGM), Self-monitoring,
45 86 technology, feasibility study, RCT, Low income countries.
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87 INTRODUCTION

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

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

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

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

1
2
3 116 hyperglycemia. The uptake of CGM devices in many high-income countries (HICs) is gradually
4
5 117 increasing, with good acceptability and clinical outcomes. A recent international consensus
6
7 118 statement on the use of CGM technology concluded that CGM data should be used for
8
9 119 therapeutic treatment decisions related to hypoglycemia and glucose variability (13).

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11
12 120 Currently, no data exist on the feasibility and clinical impact of CGM for PLWT1D in rural areas
13
14 121 of LICs especially in areas without electricity, and having low literacy and numeracy. To
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16 122 address this lack of evidence, we conducted a randomized trial to evaluate the feasibility of
17
18 123 CGM technology and clinical impact among PLWT1D with limited literacy receiving diabetes
19
20 124 care at two district hospitals in rural Malawi. This study is approved by National Health
21
22 125 Sciences Research Committee of Malawi (IRB Number IR800003905) and the Mass General
23
24 126 Brigham (IRB number 2019P003554). The protocol was previously published(1).

127 **OBJECTIVES**

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

134 **METHODS**

135 **Study setting**

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

1
2
3 146 Plus) opened at Upper Neno and Lisungwi(15-17). Patients with T1D enrolled in this clinic
4
5 147 receive care from mid-level providers with specialized non-communicable disease (NCD)
6
7 148 training. All insulin, syringes, and tools for SMBG are provided free of charge to all patients at
8
9 149 their routine monthly appointments. Every household in Neno is visited by a community
10
11 150 health worker (CHW) monthly for education and screening for multiple common conditions,
12
13 151 enrolment into maternal and chronic care, and accompaniment to the clinic(18).

14 152

16 153 **Study Participants**

17
18 154 Eligibility criteria for this study included a clinical diagnosis of T1D from any age group, in
19
20 155 diabetes care for at least one year, and seeking care at either of the PIH-supported MOH
21
22 156 hospitals. Exclusion criteria included pregnancy, mental impairment, and the inability of the
23
24 157 subject or care provider to use a CGM device. Figure 1 shows the flow diagram of the
25
26 158 recruitment process.

27 159

28
29 160 Each participant was required to complete an informed consent/ assent (children <18 years
30
31 161 of age) form on the day of the enrolment. Study staff were trained to assist patients with
32
33 162 limited literacy with the consent process.

34 163

36 164 **Design**

38 165 Randomization

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41 166 All 45 participants known to have T1D and seeking care at hospitals in Neno met the study
42
43 167 criteria and were approached for willingness to participate in this study. All agreed and were
44
45 168 randomly assigned via a random numbers table to either of the two arms: CGM (Dexcom G6,
46
47 169 Dexcom, Inc.) arm and usual care arm (using blood glucose meter) in a 2:1 ratio. Study
48
49 170 investigators and personnel were masked to the randomization sequence which was created
50
51 171 by a senior researcher.

52 172

54 173 Provider training

55
56 174 Clinical providers were required to complete one month of virtual training on routine diabetes
57
58 175 care and understanding CGM in the management of diabetes performed by the study team
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3 176 (including two nurse practitioners and one physician trained in T1D care). Then, providers
4
5 177 completed a two-week in-person hands-on training where they were required to wear a CGM
6
7 178 and learn how to use Clarity (Dexcom CGM software). Providers were trained to review data
8
9 179 from CGM downloads and SMBG logbook data and make individualized dose adjustments,
10
11 180 changes in alarm alerts on the CGM reader, and recommendations for lifestyle and insulin
12
13 181 dosing as per usual practice. Clear protocols warranting medical attention were supplied to
14
15 182 the providers, and any reported adverse events were immediately assessed and documented.
16
17 183 Provider training focused on: glucose targets; goal of time in range (TIR), insulin dosing
18
19 184 techniques and principles; basics of insulin therapy and meal planning; understanding signs
20
21 185 and strategies for managing hypoglycemia and hyperglycemia; understanding sick day
22
23 186 management; understanding food insecurity and insulin dose adjustments; and
24
25 187 troubleshooting common problems with Dexcom devices.

25 188 26 27 189 *Intervention*

28
29 190 Participants in the CGM arm were provided with a transmitter, a receiver, and sensors
30
31 191 (Dexcom G6) inserted under the skin using an applicator to wear real-time continuous
32
33 192 glucose monitoring technology for three months. All CGM equipment was provided free by
34
35 193 Dexcom. Each transmitter had a shelf life of 90 days and each sensor had a shelf life of 10
36
37 194 days after which a new sensor needs to be applied. Participants in the CGM arm were
38
39 195 instructed to use CGM daily and were advised to either change the sensor on their own or
40
41 196 follow up after ten days for new sensor insertion. Individualized clinical recommendations
42
43 197 were made by their providers at each visit using standardized material developed for the
44
45 198 study based on Dexcom training materials (Appendix A). Participants in the CGM arm
46
47 199 received a Chichewa-language handout at the beginning of the study to educate them about
48
49 200 the features of CGM and readings obtained from the reader.

50 201

51 202 *Comparator*

52
53 203 Participants in the usual care arm were asked to perform home blood glucose monitoring
54
55 204 using Safe Accu glucose meters and test strips at least once daily and record in the logbooks
56
57 205 as per established protocol(19). Providers were encouraged to review retrospective glucose
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3 206 data using SMBG logbook with participants and use the data to adjust insulin and lifestyle
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5 207 recommendations for individualized management.
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9 209 *Both Arms*

10 210 The study staff provided guidelines for routine diabetes management and education to
11 211 participants in both arms. Follow-up visits for both arms occurred monthly on the usual
12 212 clinic schedule. The CGM group had additional visits for new sensor insertion and data
13 213 downloads. Study staff had phone calls with participants to review for any severe adverse
14 214 events during the study. Participants in both groups received financial compensation for
15 215 travel to the clinic for each study visit. All diabetes and testing materials were provided free
16 216 to all participants.
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23 217

24 25 218 **Data collection and interviews**

26 219 Quality of life and HbA1c were measured at baseline and the end of the study using the WHO
27 220 Quality of Life questionnaire and a point of care HbA1c testing device, respectively. At each
28 221 visit, logbooks for those in the usual care arm and Clarity reports for those in the CGM arm
29 222 were reviewed. Five participants from each arm were interviewed by the study staff at
30 223 baseline and endline to discuss their satisfaction with content, use, complexity, comfort, and
31 224 challenges of CGM and glucose meter technology in their setting. Five providers were
32 225 interviewed regarding their opinions on both technologies. The recruitment of study
33 226 participants began in March 2022 and data collection was completed by July 2022.
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44 229 **Outcomes**

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46 230 Primary outcomes were split into implementation outcomes, defined using the Proctor (20)
47 231 framework, and clinical outcomes.
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51 233 Implementation outcomes

52 234 *Fidelity*

53 235 Fidelity is defined here using variables reflecting patients' adherence to the technology
54 236 used(20). In the CGM arm, fidelity was defined by number of sensors worn, the percent of
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3 237 time sensors were worn (based on Clarity reports), and times that dose or lifestyle
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5 238 adjustments were made. In the usual care arm, fidelity was defined as the percent of
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7 239 expected blood glucose readings logged, the percent of participants who brought logbooks
8
9 240 to the clinic during the study period, percent of expected times blood glucose test was
10
11 241 performed, the number of times insulin adjustments were made, and how often lifestyle
12
13 242 adjustments were suggested.

14 243

16 244 *Appropriateness*

17
18 245 Appropriateness was defined as the perceived fit and relevance or compatibility of
19
20 246 CGM(20). This was based on sensor problems, reporting of technological issues, and
21
22 247 qualitative interviews.

23 248

25 249 *Clinical outcomes*

27 250 *Change in HbA1c*

28
29 251 Change in Hba1c was measured as the change from baseline to endline measured using PTS
30
31 252 diagnostics A1CNow+ point of care test kits.

32 253

34 254 *Severe adverse events*

35
36 255 Severe adverse events were measured from patient self-reports, CGM or home glucose
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38 256 meters, or clinician reports.

39 257

41 258 *Secondary outcomes*

43 259 *Implementation outcomes*

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45 260 Acceptability was defined using Proctor's framework as the perception that CGM was
46
47 261 agreeable, palatable, or satisfactory (20). This was measured through qualitative interviews
48
49 262 with PLWT1D and providers.

50 263

52 264 *Clinical outcomes*

53
54 265 We were only able to measure TIR in the CGM arm, which was calculated using downloaded
55
56 266 CGM data. We defined "in range" as blood glucose reading between 70 mg/dL and 180
57
58 267 mg/dL(21). "Very high" was defined as over 250 mg/dL, and "very low" as below 54 mg/dL.

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

270

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

276

277 **Statistical methods**

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

283

284 HbA1c analysis

285 To test whether the change in HbA1c differed between the CGM and usual care arms, we
286 used longitudinal analysis of covariance—equivalent to the linear regression model specified
287 below, where HbA1c at follow-up ($HbA1c_{t1}$) is predicted by study arm (SA), HbA1c at
288 baseline ($HbA1c_{t0}$), facility site (Site), age (Age), female gender (Fem), diagnosis year (DY),
289 and body mass index (BMI). The coefficient on study arm, β_1 , was the parameter of interest.

$$290 \quad HbA1c_{t1} = \beta_0 + SA\beta_1 + HbA1c_{t0}\beta_2 + Site\beta_3 + Age\beta_4 + Fem\beta_5 + DY\beta_6 + BMI\beta_7 + \varepsilon$$

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

294

295 Quality of life analysis

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

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3 299 interval for the estimated difference in the change between the arms from the fully
4
5 300 adjusted model, adjusting for the same variables as in the HbA1c analysis described above
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7 301 except for BMI.

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10 303 Percent of time worn and time in range analyses

11 304 This CGM device measures glucose levels roughly every five minutes. We summarized the
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13 305 measurements in several ways. First, we calculated the proportion of expected observations
14
15 306 that were missing values. We did this by dividing time into five-minute increments. If no
16
17 307 observation was present for a period longer than 5.06 minutes, we considered each five-
18
19 308 minute increment between the previous and subsequent observations as missing. Then, we
20
21 309 calculated the proportion of all observations that were missing. We calculated the
22
23 310 proportion of non-missing observations within the desired blood glucose range (70 to 180
24
25 311 mg/dL) to estimate time in range, as well as the proportion that were very low (under 54
26
27 312 mg/dL), low (54 mg/dL to 69 mg/dL), high (181 mg/dL -250 mg/dL), and very high (over 250
28
29 313 mg/dL). We additionally calculated the mean and interquartile range of the non-missing
30
31 314 observations.

32
33 315

34 316 The CGM sensors lasted 10 days, but many patients returned to the clinic every 14 days to
35
36 317 obtain replacement sensors. Therefore, a substantial proportion of the missingness was
37
38 318 related to timing of sensor replacement. We estimated this proportion by assuming that any
39
40 319 missingness on the day of a sensor replacement (recorded by study clinicians) was related to
41
42 320 the replacement, and any missingness contiguous with (i.e., no non-missing observations
43
44 321 between) and prior to (including in previous days) that period of missingness was
45
46 322 categorized as related to the sensor replacement. We then tabulated the proportion of
47
48 323 missing observations related to sensor replacement. Not all individuals experienced long
49
50 324 periods missing a sensor, as some felt comfortable replacing sensors at home and were
51
52 325 given extra sensors by study staff.

53 326

54 327 **Qualitative methods**

55
56 328 We conducted a series of semi-structured interviews with 10 patients (five in each arm) at the
57
58 329 beginning and end of the study. We also interviewed five providers (two nurses and three
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60

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3 330 clinicians) who provided care to the patients during the study period. Trained members of the
4
5 331 study team conducted all interviews. Provider interviews were conducted in English. Patient
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7 332 interviews were conducted in Chichewa, and translated by a bilingual researcher. All
8
9 333 interviews were audio recorded and transcribed by a trained researcher. Interviews were
10
11 334 coded in Dedoose and analyzed using a thematic framework using a-priori themes.

12 335

13 14 336 **Deviations from protocol**

15
16 337 We initially planned a two-day training for participants, with one day devoted to
17
18 338 comprehensive T1D education. However, due to long distances needed to travel for
19
20 339 participants and resulting missed school and work, two consecutive days was not feasible.
21
22 340 Instead, for two months before the start of the study, providers gave enhanced diabetes
23
24 341 education to all participants. In the protocol outcomes, we had stated the percent of expected
25
26 342 times CGM and SMBG information was used to inform lifestyle-adjusted interventions, and
27
28 343 we were unable to determine the percent so we used number of times instead.

29 344

30 31 345 **Patient and public involvement**

32
33 346 PLWT1D were engaged throughout the study. Three of the outcomes of this research were
34
35 347 feasibility, acceptability, and appropriateness, so much of the study involved gaining
36
37 348 perspectives, experiences and views of the technology by PLWT1D. Two of the study
38
39 349 coauthors (GF & AG) are living with T1D, and were involved throughout the design of the
40
41 350 protocol, tools, training and implementation of the study.

42 351

43 44 352 **RESULTS**

45 46 353 **Participants**

47
48 354 There were 45 individuals with T1D meeting the inclusion criteria at the two eligible
49
50 355 hospitals. When approached by phone, all agreed to be included and were randomized, 30
51
52 356 to the CGM arm and 15 to the UC arm. On the day of trial initiation, one from the CGM arm
53
54 357 and two from the UC arm did not present and therefore did not participate. At the end of
55
56 358 the study, one participant in the CGM arm and two from the UC arm were not present for
57
58 359 their final evaluations and were considered lost to follow-up (Figure 1). The trial was
59
60 360 initiated on April 11th 2022 in Lisungwi district hospital and April 14th 2022 in Upper Neno

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

363

364 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

367 Primary Outcomes

368 Implementation outcomes

369 Fidelity

370 Major fidelity outcomes are seen in Table 2 and Figure 2. There was a higher rate of
 371 consultations in the CGM arm (mean 8.3) compared to the usual care arm (1.3). In the CGM
 372 arm, participants used a mean of 6.8 sensors over the study period, with a range of 2 to 9
 373 sensors. The average participant had recordings taken by their sensors for 63.8% of the
 374 time (median: 65.5%, interquartile range: 49.9-75.6%). A sensitivity analysis done dropping
 375 two individuals with only two days of observation made little change to the result (average
 376 63.5% median: 65.5% IQR 49.3-t5.7%). As many participants were unable to change the
 377 sensor on their own, and clinic days were only once a week, there was, on average, a four-
 378 day lag between one sensor ending and the next sensor being applied. We estimated the
 379 amount of each individual's missingness due to this four-day lag and found that, on average,
 380 72.7% of the missingness was due to lags between sensor changes (median: 83.4%,

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

386

387 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
<i>CGM arm</i>		
Sensors worn, mean (range)	6.8 (2,9)	
Percent of time worn, mean (SD)	63.8 (16.1)	
<i>Usual care arm</i>		
Consultations with logbook brought to clinic (%)	75.0	
Readings logged (%)	51.3	

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

389

390 In the usual care arm, participants brought logbooks to consultations 75% of the time.

391 However, readings in logbooks corresponded to glucose meters readings only 51.3% of the
 392 time.

393

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

399

400 *Appropriateness*

1
2
3 401 Over the course of the trial, only one participant in the trial arm was able to change the
4
5 402 sensors himself. Two others felt confident to physically change the sensor but were unable
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7 403 to enter the code, so they still needed to come into the clinic to change the sensor.
8
9 404 Clinicians reported that after multiple CGM insertions, patients felt confident with the
10
11 405 application process and were able to self-apply with guidance, however they were unable to
12
13 406 correctly input the sensor codes. In total, there were 28 cases of sensor failure over the
14
15 407 three-month trial period. During the first sensor use, three individuals complained of
16
17 408 discomfort but worked with providers to find a more comfortable way of wearing them. In
18
19 409 the first month, three participants accidentally removed the sensors, but there were no
20
21 410 reported cases after the first month. There were no reported problems with the solar
22
23 411 chargers, and participants were able to use the solar chargers for light in their houses.
24

412

413 Clinical outcomes

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27 414 After three months, we observed an increase of 0.2 percentage points in HbA1c in the usual
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29 415 care arm (N= 11 as follow-up HbA1cs missing for two participants) and a reduction of 1.2
30
31 416 percentage points in the CGM arm (N=28) compared to baseline. After adjusting for baseline
32
33 417 HbA1c levels and other covariates, there was a non-significant trend towards participation
34
35 418 in CGM leading to a greater reduction in HbA1c (1.1 percentage points; 95% CI: 2.4
36
37 419 percentage point reduction to 0.3 percentage point increase) compared to usual care (Table
38
39 420 3). Throughout the study there were three hospitalizations in the CGM arm and none in the
40
41 421 usual care arm. None of the hospitalizations were attributed to the intervention. One was
42
43 422 due to a long-standing non-healing diabetic foot issue, one was due to low blood sugar due
44
45 423 to the participant having no food, and one was due to high blood glucose levels.
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424

425 **Secondary Outcomes**

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49 426 Overall, participants and providers found the CGM devices acceptable. The main reported
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51 427 complaints concerned the length of time that sensors lasted, and the alarms on the CGM
52
53 428 monitors, and some participants reported not liking the visual aspect of the sensor. We go
54
55 429 further into qualitative outcomes in our companion piece(22).
56

430

431 The average percent TIR in recorded readings (not including missing data) was 30.6% (SD
 432 16.1%) (Figure 2). Among the 27 CGM arm participants with more than one week of
 433 recorded data, the average TIR was 32.6% (SD 14.7%). Over the course of the study, there
 434 was an increase in the time in the range starting in week 6 (Supplementary Figure 1). The
 435 average time in range was 30.8% in week 1, and 38.7% in week 10. To test if this increase in
 436 TIR was due to drop off of non-compliant participants, we conducted a sensitivity analysis
 437 looking at only participants who we had data for at 10 weeks. Among the 20 participants
 438 with greater than 5% non-missing data in week 10, the average time in range in week 1 was
 439 34.5%, and the average in week 10 was 37.5% (Supplementary Figure 1).

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

445 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

446 Model 1 adjusted for baseline HbA1c only; Model 2 adjusted for baseline HbA1c, facility site,
 447 age, sex, diagnosis year, and BMI. Note: 28 of the original 29 were included from the CGM
 448 arm because 1 person did not have a follow-up HbA1c measurement, and 11 of 13 were
 449 included in the usual care arm because of missing follow-up measures.

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

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

458 **DISCUSSION**

459 **Summary of main results**

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

475

476 **Comparisons with other studies**

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

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2
3 489 children and young adults affected by T1D using CGM technology (28). They found the use
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5 490 of this technology was tolerated by patients and expressed hope for wider use in the future.
6
7 491 This urban study reported an average HbA1c of 10.9% with a SD of 2.7 compared to our
8
9 492 average baseline HbA1c of 8.3% and endline HbA1c of 7.5% with a SD of 2.1. Their TIR was
10
11 493 31% compared to the TIR in our study of over 37% by week 10 (32.6% across the whole
12
13 494 study period among the 27 participants in the CGM arm with more a few days of data). All
14
15 495 three of these studies used the Freestyle Libre Pro, and users were blinded to their glucose
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17 496 data and had CGM use of 14 days. In our study we used the Dexcom G6 CGM for 90 days,
18
19 497 which provides real-time glucose data to the user and can be used to make treatment
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21 498 decisions. None of these studies examined any association between CGM use and QOL.
22

23 499
24 500 Despite challenges participants experienced with changing sensors and data missingness,
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26 501 the amount of glucose data recorded from sensor readings in this study - 63.8% of the time
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28 502 (median: 65.5%, interquartile range: 49.9-75.6% sensitivity analysis is mean: 63.5%; median:
29
30 503 65.5%; IQR; 49.3-75.7%.) and 87% when excluding missingness due to lag in sensor change –
31
32 504 is higher than data from sensor readings [mean of 51.14 days (60.9%) ($SD = 20.86$), range
33
34 505 20–81 days] in a 90-day pre- and posttest pre-experimental study with children,
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36 506 adolescents, and young adults with poorly controlled diabetes living in the U.S.(29). This
37
38 507 underscores the importance, benefits, and potential for high impact of ensuring access for
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40 508 glucose monitoring devices for PLWT1D in low-resources settings.
41

42 509

43 510 **Limitations**

44 511 This was a feasibility trial with only 42 individuals, so may not have been powered for seeing
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46 512 differences between study arms. Due to the inability of patients in the CGM arm to change
47
48 513 their device sensor, many patients ended up seeing providers twice a month compared to
49
50 514 once a month in the usual care arm, making it difficult to separate effects of technology
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52 515 versus the effect of the increased frequency of visits. Additionally, providers were excited
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54 516 about the new technology and may have paid greater attention to patients in the CGM arm.
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56 517 All participants in the study had a diagnosis of T1D, however, limited resources and a lack of
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58 518 pancreatic antibody and c-peptide testing may mean some patients were misdiagnosed.
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60 519 This study was conducted for three months. While this is far longer than other studies,

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3 520 reduction in HbA1c levels and behavior change can take longer than three months, so a
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5 521 longer study may have found greater effects. Conversely, we do not know what adherence
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7 522 would look like after three months.
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9 523

10 524 **Implications for future research and practice**

11
12 525 Our study suggests that CGM is feasible, appropriate, and acceptable in rural Malawi, and
13
14 526 may show greater effectiveness in lowering HbA1c than SMBG. We highlight the need to
15
16 527 include practical digital literacy and numeracy training for patients when considering CGM
17
18 528 as a viable clinical option in diabetes management in such settings, and future studies and
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20 529 practice should explore ways participants with low literacy can learn to change sensors
21
22 530 independently. Newer models of CGM (Dexcom G7, Freestyle Libre 2 and Freestyle Libre 3)
23
24 531 do not require sensor codes to be inputted for activation, so may be better suited to this
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26 532 setting. As devices were donated by Dexcom, this study did not examine costs, but continued
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28 533 global advocacy is necessary to ensure equitable access to intermediate T1D care for
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30 534 PLWT1D in LICs. Other studies may examine if short periods of intensive CGM use are
31
32 535 equally effective as a training tool for both patients and providers allowing a more granular
33
34 536 assessment of glycemic control than previously possible with glucose meters. In contrast,
35
36 537 other studies looking at longer lengths of time using CGM may be able to explore if this is a
37
38 538 tool that can enhance PLWT1D's understanding of their condition, improve diabetes self-
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40 539 management, decrease adverse events and diabetes-related complications, advance
41
42 540 providers' skills and knowledge, and assist with decision-making around insulin initiation for
43
44 541 people living with type 2 diabetes. Further, examining if there is added benefit and cost
45
46 542 effectiveness of real-time CGM compared to flash glucose monitoring and un-blinded CGM
47
48 543 compared to blinded in this setting is warranted.
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50 544

51 545 **CONCLUSION**

52 546 This is the first RCT conducted on CGM in a rural region of a LIC. Overall, this small
53
54 547 feasibility study conducted in one Malawian district found CGM to be feasible and
55
56 548 appropriate among PLWT1D and their health care providers. Inability of participants to
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58 549 change their own sensor is the biggest challenge, though could be addressed with use of
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60 550 newer sensor models. Although not statistically significant, the downward trend in HbA1c in

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551 study arm is promising and worth investigating over a longer period, especially in light of
552 increased TIR from baseline to endline. The current model of care needs to be strengthened
553 and TIR continues to be low — posing higher risk for acute and chronic complications among
554 this population.
555

For peer review only

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2
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4

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6

7 558

8
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10 560 Study and tool design: AJA, TR, FV, CT, GF, AM, EW, CK, GB, PP.

11 561 Training: AG, CT, GF
12

13 562 Data analysis: MMC, FV, AG, AJA, AT, LD
14

15 563 All authors contributed to the final manuscript
16

17 564 GB, TR, and AJA share senior authorship.
18

19 565
20

21 566 **COMPETING INTERESTS**
22

23 567 The authors have no competing interests.
24

25 568

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29

30 571 number 2105-04638. Dexcom generously donated CGM Dexcom 6 glucose meters and
31

32 572 sensors for the study free of charge
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Figure 1. Consort Study Flow Diagram

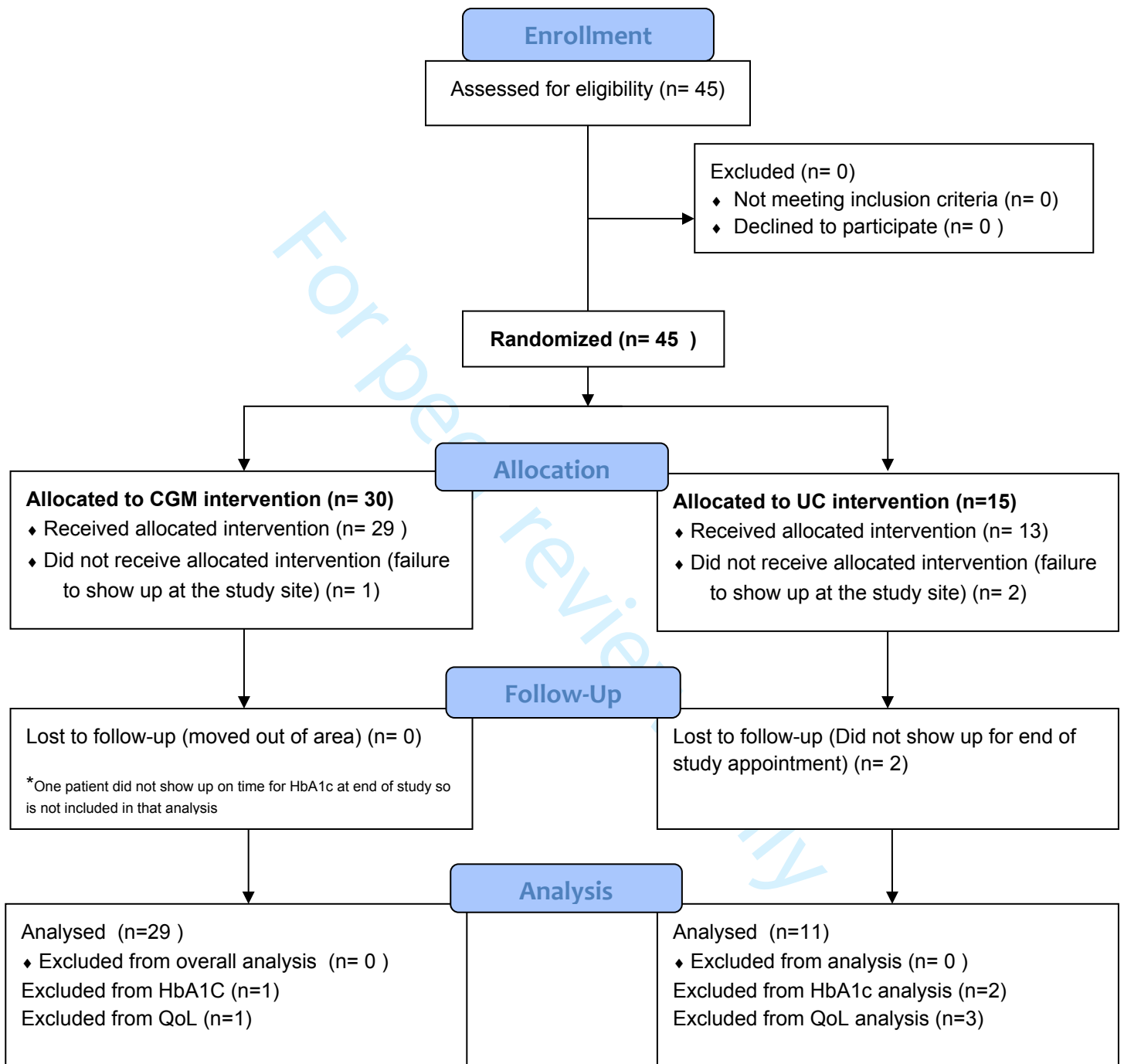
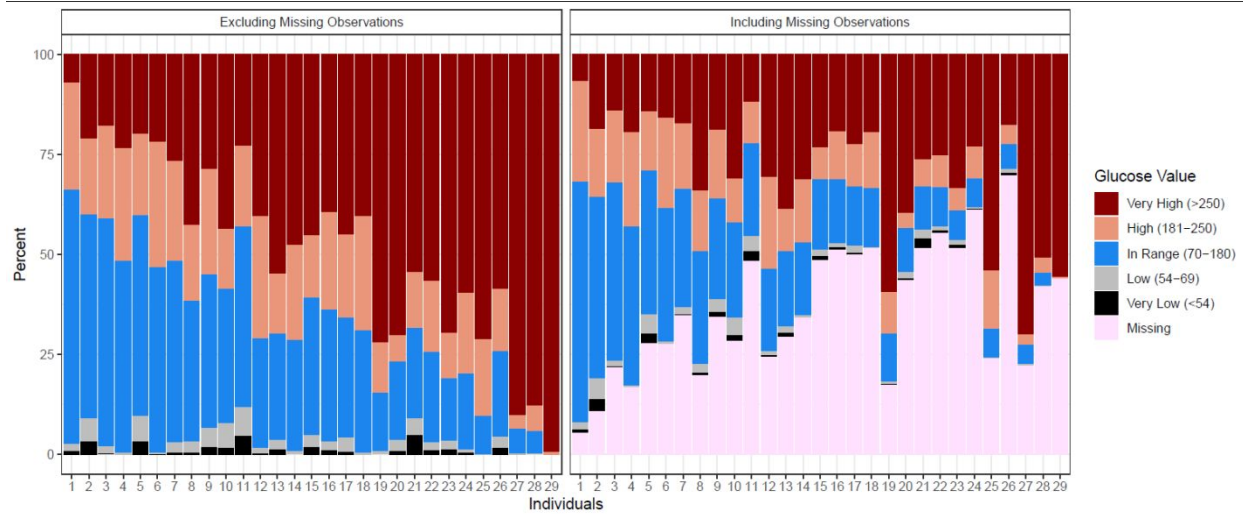


Figure 2. Time in range for each participant with missing data included and not-included



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

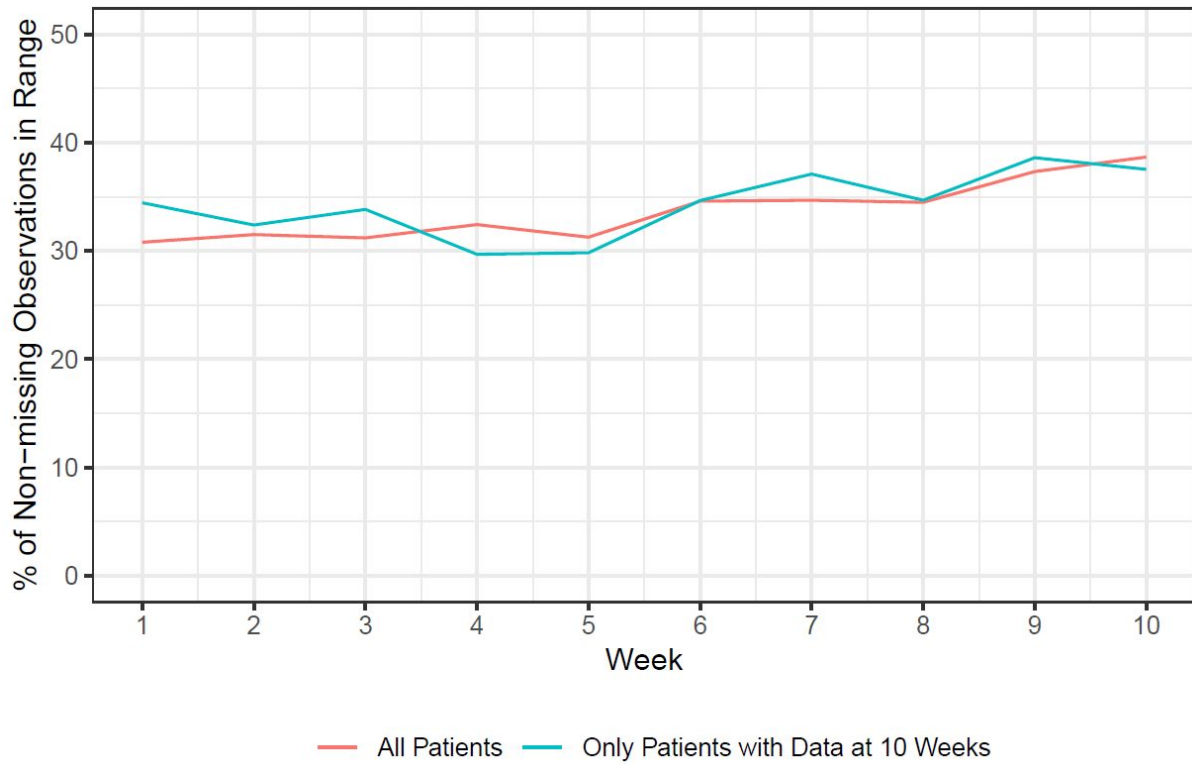
Supplementary Table 1: Quality of Life

	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)

DexcomG6
onetsetsani code ya sensor musanayambe kuika.

Kuika Sensor
Sakhani malo oyika pamimba (wazaka 2 ndi kuptiliria apo) kapena m'wamba mwamatako (zaka 2-17).
Sakhani malo omwe muli mafuta .
Pewani malo omwe muli mafupa, ziwengo, zojambula ndi malo oonekera.

1. Sambani ndi kuumitsa manja. Pukutani malo a sensor ndi thonje la spirit.
2. Chotsani zomata mata. Osakhudza zomatira.
3. Ikani choikira pakhungu.
4. Chotsani kapamwamba ndi kudina batani.
5. Chotsani choikira pakhungu.
6. Ikani choikira mujambo ndi bweretsani kuchipadala, musataye.
7. Pukutani transmitter ndi thonje la spirit.
8. Ikani transmitter m' malo mwake.
9. Modekha dinikizani transmitter ndipo mumve kulira.
10. Sisitani modinikiza katatu m' mbali mwa chomatira sensor.

Pakatha masiko 10. Chotsani transmitter.

11. Matulani kansalu m' mbalimbali mwa sensor.
12. Pidani ndi kuthyola topanila kuti muchotse transmitter.
13. Chotsani transmitter.
14. Musataye transmitter. Mutha kagwiritsa ntchito kapena Bweretsani ku chipatala.

Credits for Translation: Dester Nakotwa (NCD Nurse, Neno).

Unblinded CGM Patient Handout **dexcomG6 PRO**

Patient downloads G6 app on their smart phone to view Dexcom G6 Pro Continuous Glucose Monitoring System (G6 Pro) readings.

Healthcare professional: Insert sensor (Section A) and attach transmitter (Section B). Complete sections C and D. Review this handout with patient, then give to them to take home.

A. Insert Sensor

- 1 Gather materials: applicator, transmitter, and wipes.
- 2 Pick sensor site. Avoid bones, muscle, irritated skin, tattoos, areas that get bumped.
- 3 Clean sensor site with alcohol wipe.
- 4 Peel off adhesive backings.
- 5 Place adhesive on skin.
- 6 Fold and break off safety guard.
- 7 Press button to insert sensor.
- 8 Discard applicator. (Follow local guidelines)

B. Attach Transmitter

- 1 Clean transmitter. Only use alcohol wipe.
- 2 Insert transmitter, tab first, into holder.
- 3 Click transmitter into place, flush with holder.
- 4 Rub around patch 3 times.

C. Information patient needs for G6 app setup

- 1 Patient enters alerts settings in app
- 2 Patient enters transmitter SN in app.

Low Alert mg/dL
60 mg/dL–100 mg/dL

High Alert mg/dL
120 mg/dL–400 mg/dL

PUT STICKER HERE
Don't give transmitter SN to blinded patient

D. Transmitter removal date **Return transmitter**

In person Date

Other Time

G6 Pro Overview

G6 Pro takes your glucose reading every 5 minutes for 10 days. After returning the system, your healthcare professional reviews your glucose history and may adjust your medication, diet, or exercise.

What do I do?

- Keep your smartphone within 20 ft
- Shower and swim as normal
- Return to your healthcare professional as instructed

What don't I do?

- No MBTs
- No full-body scanners
- No sunscreen or lotions on transmitter
- No system parts in mouth, it's a choking hazard
- Don't remove transmitter, it'll end your sensor session

Continued on reverse

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

For peer review only



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:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-075554.R1
Article Type:	Original research
Date Submitted by the Author:	23-Jan-2024
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Primary Subject Heading:	Global health
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES &

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	ENDOCRINOLOGY, International health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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5 2 **Randomized control trial for the feasibility of continuous glucose monitoring in patients**
6 3 **with type 1 diabetes at two district hospitals in Neno, Malawi.**
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9 6

10 7 Apoorva Gomber^{1*}, Francis Valeta^{2*}, Matthew M Coates¹, Celina Trujillo^{1,3,5}, Gina Ferrari^{1,3},
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2
3 46 **ABSTRACT**
4 47

5 48 **Objectives:** To assess the feasibility and change in clinical outcomes associated with
6 49 Continuous Glucose Monitoring (CGM) use among a rural population in Malawi living with
7 50 type 1 diabetes **Design:** a 2:1 open randomized controlled feasibility trial

8 51 **Setting:** Two Partners In Health-supported Ministry of Health-run first level district hospitals
9 52 in Neno, Malawi

10 53 **Participants:** 45 people living with type 1 diabetes

11 54 **Interventions:** Participants were randomly assigned to Dexcom G6 CGM (n=30) use or usual
12 55 care (UC) (n=15) consisting of Safe-Accu glucose monitors and strips. Both arms received
13 56 diabetes education.

14 57 **Outcomes:** Primary outcomes included fidelity, appropriateness, change in HbA1c, and
15 58 severe adverse events. Secondary outcomes included acceptability, time in range (CGM arm
16 59 only) standard deviation of HbA1c, and quality of life.

17 60 **Results:** Participants tolerated CGM well but were unable to change their own sensors
18 61 which resulted in increased clinic visits in the CGM arm. Despite the hot climate, skin rashes
19 62 were uncommon but cut-out tape overpatches were needed to secure the sensors in place.
20 63 Participants in the CGM arm had greater numbers of dose adjustments and lifestyle change
21 64 suggestions than those in the UC arm. There was a trend towards reduction of HbA1c in the
22 65 CGM arm (-1.1% 95%CI -2.4, 0.3). Participants in the CGM arm wore their CGM on average
23 66 63.8% of the time. Participants in the UC arm brought logbooks to clinic 75% of the time.
24 67 There were three hospitalizations all in the CGM arm, but none were related to the
25 68 intervention.

26 69 **Conclusions:** This is the first RCT conducted on CGM in a rural region of a low-income
27 70 country (LIC). CGM was feasible and appropriate among PLWT1D and providers, but
28 71 inability of participants to change their own sensors is a challenge.

29 72 **Trial registration:** Trial registration number PACTR202102832069874. This study was
30 73 approved by National Health Sciences Research Committee of Malawi (IRB Number
31 74 IR800003905) and the Mass General Brigham (IRB number 2019P003554). The protocol was
32 75 previously published.

33 76
34 77 **Strengths and limitations of this study:**
35 78

- 36 79 1. Randomized controlled trial evaluating feasibility and acceptability of CGM in a rural,
37 80 low-literacy population in a low-income country
38 81 2. Study participants were followed for a period of 90 days, allowing for longitudinal data
39 82 on impact of CGM
40 83 3. Limited by small sample size
41 84

42 85
43 86
44 87
45 88 **Keywords:** Type 1 diabetes, Continuous glucose monitoring (CGM), Self-monitoring,
46 89 technology, feasibility study, RCT, Low income countries.
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90 INTRODUCTION

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

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

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

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

1
2
3 119 but not a complete picture, and neither provide real-time alerts about hypo- or
4
5 120 hyperglycemia. The uptake of CGM devices in many high-income countries (HICs) is gradually
6
7 121 increasing, with good acceptability and clinical outcomes. A recent international consensus
8
9 122 statement on the use of CGM technology concluded that CGM data should be used for
10
11 123 therapeutic treatment decisions related to hypoglycemia and glucose variability (12).

12
13 124 Currently, no data exist on the feasibility and effect on clinical outcomes of CGM for PLWT1D
14
15 125 in rural areas of LICs especially in areas without electricity, and having low literacy and
16
17 126 numeracy. To address this lack of evidence, we conducted a randomized trial to evaluate the
18
19 127 feasibility of CGM technology and change in clinical outcomes among PLWT1D with limited
20
21 128 literacy receiving diabetes care at two district hospitals in rural Malawi. This study is approved
22
23 129 by National Health Sciences Research Committee of Malawi (IRB Number IR800003905) and
24
25 130 the Mass General Brigham (IRB number 2019P003554). The protocol was previously
26
27 131 published(13).

132 **OBJECTIVES**

133 The objectives of this study are to (1) assess the feasibility and appropriateness of CGM use
134
135 134 among a rural population of PLWT1D and limited literacy in an LIC; (2) to determine if CGM
136
137 135 use can have an effect on diabetes clinical outcomes among PLWT1D in rural regions of LICs
138
139 136 and (3) determine the standard deviation of HbA1c across individuals at baseline to inform
140
141 137 further studies.

142 **METHODS**

143 **Study setting**

144 The study was conducted at two rural Ministry of Health (MOH) supported first-level hospitals
145
146 142 in Neno district, Malawi, with a population of about 138,000(14), primarily relying on
147
148 143 subsistence agriculture. Neno District Hospital is in a mountainous region near the
149
150 144 Mozambique border and Lisungwi Community Hospital is in the lower, drier area near the
151
152 145 Shire River. Both hospitals are similar in protocol and resources and are overseen by the same
153
154 146 district leadership. Since 2007, Partners In Health (PIH), a US-based non-government
155
156 147 organization known locally as Abwenzi Pa Za Umoyo (APZU), has partnered with MOH to
157
158 148 improve healthcare and socioeconomic development in Neno District. In 2018, two advanced
159
160

1
2
3 149 non-communicable disease (NCD) clinics providing high-quality care for complex NCDs,
4
5 150 consistent with the Package of essential medicines for noncommunicable diseases-Plus (PEN-
6
7 151 Plus) opened at Upper Neno and Lisungwi(15-17). Patients with T1D enrolled in this clinic
8
9 152 receive care from mid-level providers with specialized non-communicable disease (NCD)
10
11 153 training. All insulin, syringes, and tools for SMBG are provided free of charge to all patients at
12
13 154 their routine monthly appointments. PLWT1D typically use human insulin, intermediate-
14
15 155 acting (NPH) two times daily and fast- acting (regular) two to three times daily. Every
16
17 156 household in Neno is visited by a community health worker (CHW) monthly for education and
18
19 157 screening for multiple common conditions, enrolment into maternal and chronic care, and
20
21 158 accompaniment to the clinic(18).
22

23 159

24 160 **Study Participants**

25 161 Eligibility criteria for this study included a clinical diagnosis of T1D in PLWT1D, in diabetes care
26
27 162 for at least one year, and seeking care at either of the PIH-supported MOH hospitals. We did
28
29 163 not exclude anyone based on age. Exclusion criteria included pregnancy, mental impairment,
30
31 164 and the inability of the subject or care provider to use a CGM device. Figure 1 shows the flow
32
33 165 diagram of the recruitment process.
34

35 166

36 167 Each participant was required to complete an informed consent/ assent (children <18 years
37
38 168 of age) form on the day of the enrolment. Study staff were trained to assist patients with
39
40 169 limited literacy with the consent process.
41

42 170

43 171 **Design**

44 172 **Randomization**

45
46
47
48 173 All 45 participants known to have T1D and seeking care at hospitals in Neno met the study
49
50 174 criteria and were approached for willingness to participate in this study. All agreed and were
51
52 175 randomly assigned via a random numbers table to either of the two arms: CGM (Dexcom G6,
53
54 176 Dexcom, Inc.) arm and usual care arm (using blood glucose meter) in a 2:1 ratio. Study
55
56 177 investigators and personnel were masked to the randomization sequence which was created
57
58 178 by a senior researcher.
59
60

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3 1794
5 180 Provider training

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7 181 Clinical providers were required to complete one month of virtual training on routine diabetes
8
9 182 care and understanding CGM in the management of diabetes performed by the study team
10
11 183 (including two nurse practitioners and two clinical officers trained in T1D care). Then,
12
13 184 providers completed a two-week in-person hands-on training where they were required to
14
15 185 wear a CGM and learn how to use Clarity (Dexcom CGM software). Providers were trained to
16
17 186 review data from CGM downloads and SMBG logbook data and make individualized dose
18
19 187 adjustments, changes in alarm alerts on the CGM reader, and recommendations for lifestyle
20
21 188 and insulin dosing as per usual practice. Clear protocols warranting medical attention were
22
23 189 supplied to the providers, and any reported adverse events were immediately assessed and
24
25 190 documented. Provider training focused on: glucose targets; goal of time in range (TIR), insulin
26
27 191 dosing techniques and principles; basics of insulin therapy and meal planning; understanding
28
29 192 signs and strategies for managing hypoglycemia and hyperglycemia; understanding sick day
30
31 193 management; understanding food insecurity and insulin dose adjustments; and
32
33 194 troubleshooting common problems with Dexcom devices.

34

35 196 Intervention

36
37 197 Participants in the CGM arm were provided with a transmitter, a receiver, and sensors
38
39 198 (Dexcom G6) inserted under the skin using an applicator to wear real-time continuous
40
41 199 glucose monitoring technology for three months. All CGM equipment was provided free by
42
43 200 Dexcom. Each transmitter had a shelf life of 90 days and each sensor had a shelf life of 10
44
45 201 days after which a new sensor needs to be applied. Participants in the CGM arm were
46
47 202 instructed to use CGM daily and were advised to either change the sensor on their own or
48
49 203 follow up after ten days for new sensor insertion. Individualized clinical recommendations
50
51 204 were made by their providers at each visit using standardized material developed for the
52
53 205 study based on Dexcom training materials (Appendix A). Participants in the CGM arm
54
55 206 received a Chichewa-language handout at the beginning of the study to educate them about
56
57 207 the features of CGM and readings obtained from the reader.

58

59 209 *Comparator*
60

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2
3 210 Participants in the usual care arm were asked to perform home blood glucose monitoring
4
5 211 using Safe Accu glucose meters and test strips at least once daily and record in the logbooks
6
7 212 as per established protocol(19). Providers were encouraged to review retrospective glucose
8
9 213 data using SMBG logbook with participants and use the data to adjust insulin and lifestyle
10
11 214 recommendations for individualized management.

12 215

14 216 *Both Arms*

16 217 The study staff provided guidelines for routine diabetes management and education to
17
18 218 participants in both arms. Follow-up visits for both arms occurred monthly on the usual
19
20 219 clinic schedule. The CGM group had additional visits for new sensor insertion and data
21
22 220 downloads. Study staff had phone calls with participants to review for any severe adverse
23
24 221 events during the study. Participants in both groups received financial compensation for
25
26 222 travel to the clinic for each study visit. All diabetes and testing materials were provided free
27
28 223 to all participants.

29 224

31 225 **Data collection and interviews**

33 226 Quality of life and HbA1c were measured at baseline and the end of the study using the WHO
34
35 227 Quality of Life questionnaire and a point of care HbA1c testing device, respectively. At each
36
37 228 visit, logbooks for those in the usual care arm and Clarity reports for those in the CGM arm
38
39 229 were reviewed. Five participants from each arm were interviewed by the study staff at
40
41 230 baseline and endline to discuss their satisfaction with content, use, complexity, comfort, and
42
43 231 challenges of CGM and glucose meter technology in their setting. Five providers were
44
45 232 interviewed regarding their opinions on both technologies. The recruitment of study
46
47 233 participants began in March 2022 and data collection was completed by July 2022.

48 234

49 235

51 236 **Outcomes**

53 237 While the primary aim of this study is to understand the feasibility of CGM in a low resource
54
55 238 setting, it is also important to ensure that even if the technology is functional it does not
56
57 239 have negative effects on clinical outcomes for users. For that reason we include two clinical

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60

1
2
3 240 outcomes, HbA1c and time in range. Primary outcomes were split into implementation
4
5 241 outcomes, defined using the Proctor (20) framework, and clinical outcomes.
6

7 242

8
9 243 Implementation outcomes

10 244 *Fidelity*

11
12 245 Fidelity is defined here using variables reflecting patients' adherence to the technology used
13
14 246 (20). In the CGM arm, fidelity was defined by number of sensors worn, the percent of time
15
16 247 sensors were worn (based on Clarity reports), and times that dose or lifestyle adjustments
17
18 248 were made. In the usual care arm, fidelity was defined as the percent of expected blood
19
20 249 glucose readings logged, the percent of participants who brought logbooks to the clinic
21
22 250 during the study period, percent of expected times blood glucose test was performed, the
23
24 251 number of times insulin adjustments were made, and how often lifestyle adjustments were
25
26 252 suggested.
27

28 253

29 254 *Appropriateness*

30 255 Appropriateness was defined as the perceived fit and relevance or compatibility of
31
32 256 CGM(20). This was based on sensor problems, reporting of technological issues, and
33
34 257 qualitative interviews.
35

36 258

37
38 259 Clinical outcomes

39 260 *Change in HbA1c*

40
41 261 Change in Hba1c was measured as the change from baseline to endline measured using PTS
42
43 262 diagnostics A1CNow+ point of care test kits. Due to lower than expected HbA1c
44
45 263 measurements, we also included a comparison of endline HbA1c results and the 90-day
46
47 264 estimated average glucose values calculated using Clarity reports of patients in the CGM
48
49 265 arm of the study.
50

51 266

52 267 *Severe adverse events*

53
54 268 Severe adverse events were measured from patient self-reports, CGM or home glucose
55
56 269 meters, or clinician reports.
57

58 270
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60

1
2
3 271 Secondary outcomes

4
5 272 *Implementation outcomes*

6
7 273 Acceptability was defined using Proctor's framework as the perception that CGM was
8
9 274 agreeable, palatable, or satisfactory (20). This was measured through qualitative interviews
10
11 275 with PLWT1D and providers.

12 276

13
14 277 *Clinical outcomes*

15
16 278 We were only able to measure TIR in the CGM arm, which was calculated using downloaded
17
18 279 CGM data. We defined "in range" as blood glucose reading between 70 mg/dL and 180
19
20 280 mg/dL (21). "Very high" was defined as over 250 mg/dL, and "very low" as below 54 mg/dL.
21
22 281 Because two participants only had fewer than five days of CGM readings each, we included
23
24 282 a sensitivity analysis removing these participants' data.

25 283

26
27 284 The standard deviation in HbA1c was calculated using the overall HbA1c SD in the baseline
28
29 285 point-of-care tests. Quality of life (QoL) was measured using the WHO-BREF both at
30
31 286 baseline and at the end of the study. The WHO-BREF includes four domains: Physical health,
32
33 287 psychological, social relationships, and environment. QoL was calculated both by individual
34
35 288 domain and overall.

36 289

37
38 290 **Statistical methods**

39
40 291 Statistical analyses were conducted using R version 4.2.2, or Stata version 14. We did not
41
42 292 conduct sample size calculations because we recruited all PLWT1D receiving care at two
43
44 293 PIH-assisted hospitals where this study was being conducted. Rather, we calculated power
45
46 294 to detect the difference in HbA1c with the number of patients who participated (29 in the
47
48 295 CGM arm and 13 in the usual care arm). Given a pooled standard deviation of 2.05 and an
49
50 296 alpha level of 0.05, we had 80% power to detect a 1.96 percentage point difference in
51
52 297 HbA1c between the two study arms in a two-sample t-test. Initial power calculations relied
53
54 298 on a larger number of expected participants (13). We conducted analysis as intention to
55
56 299 treat.

57 300

58 301 HbA1c analysis

59
60

1
2
3 302 To test whether the change in HbA1c differed between the CGM and usual care arms, we
4
5 303 used the linear regression model specified below, equivalent to longitudinal analysis of
6
7 304 covariance, where HbA1c at follow-up ($HbA1c_{t1}$) is predicted by study arm (SA), HbA1c at
8
9 305 baseline ($HbA1c_{t0}$), facility site (Site), age (Age), female gender (Fem), diagnosis year (DY),
10
11 306 and body mass index (BMI), with an error term, ε , assumed normally distributed. The
12
13 307 coefficient on study arm, β_1 , was the parameter of interest.

$$14 \quad 308 \quad HbA1c_{t1} = \beta_0 + SA\beta_1 + HbA1c_{t0}\beta_2 + Site\beta_3 + Age\beta_4 + Fem\beta_5 + DY\beta_6 + BMI\beta_7 + \varepsilon$$

15
16 309 We report the point estimate and 95% confidence interval for this parameter estimate from
17
18 310 the fully adjusted model above as well as a minimally adjusted model, only including the
19
20 311 terms for study arm and baseline HbA1c.

21
22 312
23 313 To test the relatively low HbA1c levels we compared the difference between endline HbA1c
24
25 314 results and the 90-day estimated average glucose values for participants in the CGM arm.
26
27 315 Estimated average glucose (EAG) was calculated in the Clarity application. The standard
28
29 316 formula of $EAG \text{ (mg/dL)} = 28.7 \times A1c - 46.7$ was used to convert EAG to estimated HbA1c
30
31 317 (34). Paired t-test was used to compare the estimated HbA1c to the point-of-care HbA1c.

32
33 318
34 319 Quality of life analysis

35
36 320 To estimate the difference in the change in QoL between study arms, we used the same
37
38 321 approach as for HbA1c. We conducted a regression for each of the four domains of the
39
40 322 WHO-BREF as well as the overall score, reporting the point estimate and 95% confidence
41
42 323 interval for the estimated difference in the change between the arms from the fully
43
44 324 adjusted model, adjusting for the same variables as in the HbA1c analysis described above
45
46 325 except for BMI.

47 326
48
49 327 Percent of time worn and time in range analyses

50
51 328 This CGM device measures glucose levels roughly every five minutes. We summarized the
52
53 329 measurements in several ways. First, we calculated the proportion of expected observations
54
55 330 that were missing values. We did this by dividing time into five-minute increments. If no
56
57 331 observation was present for a period longer than 5.06 minutes, we considered each five-
58
59 332 minute increment between the previous and subsequent observations as missing. Then, we
60

1
2
3 333 calculated the proportion of all observations that were missing. We calculated the
4
5 334 proportion of non-missing observations within the desired blood glucose range (70 to 180
6
7 335 mg/dL) to estimate time in range, as well as the proportion that were very low (under 54
8
9 336 mg/dL), low (54 mg/dL to 69 mg/dL), high (181 mg/dL -250 mg/dL), and very high (over 250
10
11 337 mg/dL). We additionally calculated the mean and interquartile range of the non-missing
12
13 338 observations.

14 339

16 340 The CGM sensors lasted 10 days, but many patients returned to the clinic every 14 days to
17
18 341 obtain replacement sensors. Therefore, a substantial proportion of the missingness was
19
20 342 related to timing of sensor replacement. We estimated this proportion by assuming that any
21
22 343 missingness on the day of a sensor replacement (recorded by study clinicians) was related to
23
24 344 the replacement, and any missingness contiguous with (i.e., no non-missing observations
25
26 345 between) and prior to (including in previous days) that period of missingness was
27
28 346 categorized as related to the sensor replacement. We then tabulated the proportion of
29
30 347 missing observations related to sensor replacement. Not all individuals experienced long
31
32 348 periods missing a sensor, as some felt comfortable replacing sensors at home and were
33
34 349 given extra sensors by study staff.

34 350

36 351 **Qualitative methods**

38 352 We conducted a series of semi-structured interviews with 10 patients (five in each arm) at the
39
40 353 beginning and end of the study. We also interviewed five providers (two nurses and three
41
42 354 clinicians) who provided care to the patients during the study period. Trained members of the
43
44 355 study team conducted all interviews. Provider interviews were conducted in English. Patient
45
46 356 interviews were conducted in Chichewa, and translated by a bilingual researcher. All
47
48 357 interviews were audio recorded and transcribed by a trained researcher. Interviews were
49
50 358 coded in Dedoose and analyzed using a thematic framework using a-priori themes.

51 359

52 360 **Deviations from protocol**

54 361 We initially planned a two-day training for participants, with one day devoted to
55
56 362 comprehensive T1D education. However, due to long distances needed to travel for
57
58 363 participants and resulting missed school and work, two consecutive days was not feasible.

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

368

369 **Patient and public involvement**

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

375

376 **RESULTS**

377 **Participants**

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

387

388 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 (%)			

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390

	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
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	<i>CGM</i> (N=29)	<i>Usual care</i> (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
<i>CGM arm</i>		
Sensors worn, mean (range)	6.8 (2,9)	
Percent of time worn, mean (SD)	63.8 (16.1)	
<i>Usual care arm</i>		
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

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3 432 discomfort but worked with providers to find a more comfortable way of wearing them. In
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5 433 the first month, three participants accidentally removed the sensors, but there were no
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7 434 reported cases after the first month. Rashes and skin irritation were not a commonly
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9 435 encountered complaint in the CGM arm. The hot weather caused a few participants
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11 436 difficulty with keeping the sensor attached. We overcame this using skin Tac adhesive and
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13 437 cut-out tape overpatches to secure the sensors in place and prevent removal. No sensor
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15 438 related bleeding or potential skin reaction around or under the sensor was observed. There
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17 439 were no reported problems with the solar chargers, and participants were able to use the
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19 440 solar chargers for light in their houses.
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21 441

22 442 Clinical outcomes

23 443 After three months, we observed an increase of 0.2 percentage points in HbA1c in the usual
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25 444 care arm (N= 11 as follow-up HbA1cs missing for two participants) and a reduction of 1.2
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27 445 percentage points in the CGM arm (N=28) compared to baseline. After adjusting for baseline
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29 446 HbA1c levels and other covariates, participation in CGM compared to usual care was
30
31 447 associated with a 1.1 percentage point lower HbA1c; confidence intervals were compatible
32
33 448 with a moderate to null reduction in the CGM arm relative to the usual care arm (95% CI: 2.4
34
35 449 percentage point reduction to 0.3 percentage point increase, Table 3). Throughout the study
36
37 450 there were three hospitalizations in the CGM arm and none in the usual care arm. None of
38
39 451 the hospitalizations were attributed to the intervention. One was due to a long-standing
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41 452 non-healing diabetic foot issue, one was due to low blood sugar due to the participant
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43 453 having no food, and one was due to high blood glucose levels.
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45 454

45 455 Mean endline point-of-care HbA1c was 7.4% (95% CI 6.6%, 8.1%). Mean estimated HbA1c
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47 456 was significantly higher, at 10.1% (95% CI 9.3%, 10.8%) and mean difference of 2.7% (95% CI
48
49 457 2.2%, 3.2%; $p < 0.05$). Supplementary Figure 1 shows point-of-care HbA1c and estimated
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51 458 HbA1c for each participant in the CGM arm.
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53 459

54 460 **Secondary Outcomes**

56 461 Overall, participants and providers found the CGM devices acceptable. The main reported
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58 462 complaints concerned the length of time that sensors lasted, and the alarms on the CGM
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60

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

465
466 The average percent TIR in recorded readings (not including missing data) was 30.6% (SD
467 16.1%) (Figure 2). Among the 27 CGM arm participants with more than one week of
468 recorded data, the average TIR was 32.6% (SD 14.7%). Over the course of the study, there
469 was an increase in the time in the range starting in week 6 (Supplementary Figure 2). The
470 average time in range was 30.8% in week 1, and 38.7% in week 10. To examine whether this
471 increase in TIR was due to drop off of non-compliant participants, we conducted a sensitivity
472 analysis looking at only participants who we had data for at 10 weeks. Among the 20
473 participants with greater than 5% non-missing data in week 10, the average time in range in
474 week 1 was 34.5%, and the average in week 10 was 37.5% (Supplementary Figure 2).

475
476 Pretrial, there was a standard deviation of 2.1 in HbA1c pooled across two arms, although
477 baseline HbA1c was low overall compared to what is generally expected in this type of
478 setting(23-25).

479

480 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

481 Model 1 adjusted for baseline HbA1c only; Model 2 adjusted for baseline HbA1c, facility site,
482 age, sex, diagnosis year, and BMI. Note: 28 of the original 29 were included from the CGM
483 arm because 1 person did not have a follow-up HbA1c measurement, and 11 of 13 were
484 included in the usual care arm because of missing follow-up measures.

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

486

487 Over the course of the study, QoL (N=28 in CGM and N=10 in UC) was assessed using WHO-
488 BREF increased across all domains (Supplementary Table 1). Though unadjusted QoL

489 increased slightly more in the UC arm (9.0) than the CGM arm (6.7), confidence intervals for

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3 490 differences in the change in QoL between groups were large, and we did not find any strong
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5 491 evidence of differences.
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10 494 **DISCUSSION**

11 495 **Summary of main results**

12 496 This is the first RCT to be carried out in a rural area of a LIC on the feasibility of CGM. While
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14 497 participants wore their sensors just under two-thirds of the time, much of the missingness
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16 498 (over 70% on average) was attributable to their inability to change their sensors. The most
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18 499 pervasive barrier to CGM use among patients was the reported limited digital literacy and
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20 500 confidence with the sensor application process, which required patients in the CGM arm to
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22 501 come more frequently into the clinic than the usual care arm. However, with time and
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24 502 multiple CGM insertions, patients felt confident with the application process and could self-
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26 503 apply under the guidance of the clinicians, but still needed help with numerically entering
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28 504 sensor codes to activate them. Skin rashes were not a notable complaint, although due to the
29
30 505 hot weather there was some difficulty with sensor adhesion that was rectified by using skin
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32 506 Tac adhesive and cut-out tape overpatches to secure the sensors in place. After the first few
33
34 507 weeks, participants tolerated the CGM well, and clinicians were far more likely to make dose
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36 508 adjustments in the CGM arm than the usual care arm. There was a trend towards greater
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38 509 reduction in HbA1C in the CGM arm than in the usual care arm. However, there were many
39
40 510 more consultations in the CGM arm, so it is difficult to attribute the improvement to the CGM
41
42 511 or the greater number of consultations. Given the four-day lag between sensor end and
43
44 512 replacement, the reduction may have been greater without this lag. The intervention was
45
46 513 deemed acceptable by participants with the greatest complaint being around sensor beeping.
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48 514

49 515 **Comparisons with other studies**

50 516 This is the first RCT conducted in a rural setting in a LIC to assess the feasibility of CGM and
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52 517 its effect on clinical outcomes and quality of life among people living with T1D. To date,
53
54 518 there are less than a handful of studies on CGM use in the African continent, none of which
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56 519 are randomized control trials. One of these studies evaluated the glycemic profile – glucose
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58 520 exposure, variability, stability, and risk of hypoglycemia – of people living with T1D and T2D
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3 521 in South Africa, across 16 different clinics(26). In Uganda, Niwaha and colleagues conducted
4 522 a study to assess the risk of hypoglycemia for people living with T2D being treated with
5 523 sulphonylureas or insulin and did not include PLWT1D(27). While the study in South Africa
6 524 mentioned that some sensors failed to record data, neither this study nor that of Niwaha
7 525 looked specifically at fidelity, appropriateness, or acceptability. A short observational study
8 526 by McClure Yauch and Velazquez (2020) was conducted at national referral hospitals in
9 527 urban areas in Kenya and Uganda to assess feasibility of CGM use and the glycemic profile of
10 528 children and young adults affected by T1D using CGM technology (28). They found the use
11 529 of this technology was tolerated by patients and expressed hope for wider use in the future.
12 530 This urban study reported an average HbA1c of 10.9% with a SD of 2.7 compared to our
13 531 average baseline HbA1c of 8.3% and endline HbA1c of 7.5% with a SD of 2.1. Their TIR was
14 532 31% compared to the TIR in our study of over 37% by week 10 (32.6% across the whole
15 533 study period among the 27 participants in the CGM arm with more a few days of data). All
16 534 three of these studies used the Freestyle Libre Pro, and users were blinded to their glucose
17 535 data and had CGM use of 14 days. In our study we used the Dexcom G6 CGM for 90 days,
18 536 which provides real-time glucose data to the user and can be used to make treatment
19 537 decisions. None of these studies examined any association between CGM use and QOL.
20 538
21 539 Comparison of endline point-of-care HbA1c to estimated HbA1c based on CGM values
22 540 showed that point-of-care HbA1c may be overestimating glycemic control—A few theories
23 541 for the discrepancy between HbA1c and mean blood glucose levels have been proposed,
24 542 including the presence of hemoglobinopathies, individual variations in the lifespan of red
25 543 blood cells, renal impairment, and nutritional deficiencies (e.g., iron-deficiency anemia,
26 544 Kwashiorkor, Marasmus) (29,30). No hemoglobinopathies are present in this patient
27 545 population. Additionally, numerous assays for point-of-care HbA1c testing have become
28 546 available over the last decade of possibly varying quality. These findings reinforce that
29 547 HbA1c alone may not be adequate to evaluate glycemic control in PLWT1D, adding to
30 548 current literature highlighting the importance of availability for additional ways to evaluate
31 549 glycemic control, such as SMBG or CGM.
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3 551 Despite challenges participants experienced with changing sensors and data missingness,
4 552 the amount of glucose data recorded from sensor readings in this study - 63.8% of the time
5 553 (median: 65.5%, interquartile range: 49.9-75.6% sensitivity analysis is mean: 63.5%; median:
6 554 65.5%; IQR; 49.3-75.7%.) and 87% when excluding missingness due to lag in sensor change –
7 555 is higher than data from sensor readings [mean of 51.14 days (60.9%) ($SD = 20.86$), range
8 556 20–81 days] in a 90-day pre- and posttest pre-experimental study with children,
9 557 adolescents, and young adults with poorly controlled diabetes living in the U.S.(31). This
10 558 underscores the importance, benefits, and potential for high impact of ensuring access for
11 559 glucose monitoring devices for PLWT1D in low-resources settings.
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22 561 **Limitations**

23 562 This was a feasibility trial with only 42 individuals, it was not powered for seeing differences
24 563 between study arms in outcomes like HbA1c and QoL. Due to the inability of patients in the
25 564 CGM arm to change their device sensor, many patients ended up seeing providers twice a
26 565 month compared to once a month in the usual care arm, making it difficult to separate
27 566 effects of technology versus the effect of the increased frequency of visits. Additionally,
28 567 providers were excited about the new technology and may have paid greater attention to
29 568 patients in the CGM arm. All participants in the study had a diagnosis of T1D, however,
30 569 limited resources and a lack of pancreatic antibody and C-peptide testing may mean some
31 570 patients were misdiagnosed. This study was conducted for three months. While this is far
32 571 longer than other studies, reduction in HbA1c levels and behavior change can take longer
33 572 than three months, so a longer study may have found greater effects. Conversely, we do not
34 573 know what adherence would look like after three months.
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47 575 **Implications for future research and practice**

48 576 Our study suggests that CGM is feasible, appropriate, and acceptable in rural Malawi, and
49 577 may show greater effectiveness in lowering HbA1c than SMBG. We highlight the need to
50 578 include practical digital literacy and numeracy training for patients when considering CGM
51 579 as a viable clinical option in diabetes management in such settings, and future studies and
52 580 practice should explore ways participants with low literacy can learn to change sensors
53 581 independently. Newer models of CGM (Dexcom G7, Freestyle Libre 2 and Freestyle Libre 3)
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3 582 do not require sensor codes to be inputted for activation, so may be better suited to this
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5 583 setting. As devices were donated by Dexcom, this study did not examine costs, but
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7 584 continued global advocacy is necessary to ensure equitable access to intermediate T1D care
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9 585 for PLWT1D in LICs. Other studies may examine if short periods of intensive CGM use are
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11 586 equally effective as a training tool for both patients and providers allowing a more granular
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13 587 assessment of glycemic control than previously possible with glucose meters. In contrast,
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15 588 other studies looking at longer lengths of time using CGM may be able to explore if this is a
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17 589 tool that can enhance PLWT1D's understanding of their condition, improve diabetes self-
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19 590 management, decrease adverse events and diabetes-related complications, advance
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21 591 providers' skills and knowledge, and assist with decision-making around insulin initiation for
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23 592 people living with type 2 diabetes. Further, examining if there is added benefit and cost
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25 593 effectiveness of real-time CGM compared to flash glucose monitoring and un-blinded CGM
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27 594 compared to blinded in this setting is warranted.
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30 596 **CONCLUSION**

31 597 This is the first RCT conducted on CGM in a rural region of a LIC. Overall, this small
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33 598 feasibility study conducted in one Malawian district found CGM to be feasible and
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35 599 appropriate among PLWT1D and their health care providers. Inability of participants to
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37 600 change their own sensor is the biggest challenge, though could be addressed with use of
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39 601 newer sensor models. Although not statistically significant, the downward trend in HbA1c in
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41 602 study arm is promising and worth investigating over a longer period, especially in light of
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43 603 increased TIR from baseline to endline. The current model of care needs to be strengthened
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45 604 and TIR continues to be low — posing higher risk for acute and chronic complications among
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47 605 this population.
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3 607 **ACKNOWLEDGMENTS**

4
5 608 Roy Beck for advice on trial design.

6
7 609

8
9 610 **CONTRIBUTIONS**

10 611 Study and tool design: AJA, TR, FV, CT, GF, AM, EW, CK, GB, PP.

11 612 Training: AG, CT, GF

12 613 Data analysis: MMC, FV, AG, AJA, AT, LD

13 614 All authors contributed to the final manuscript

14 615 GB, TR, and AJA share senior authorship.

15 616

16 617 **COMPETING INTERESTS**

17 618 The authors have no competing interests.

18 619

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21 622 number 2105-04638. Dexcom generously donated CGM Dexcom 6 glucose meters and

22 623 sensors for the study free of charge.

23 624

24 625 **DATA AVAILABILITY STATEMENT**

25 626 De-identified data are available upon reasonable request from the corresponding author

26 627 (AJA) at aadler2@bwh.harvard.edu.

27 628

28 629 **FIGURES LEGEND**

29 630 Figure 1: Consort study flow diagram

30 631 Figure 2: Time in range for each participant with missing data included and not included

31 632 Figure 2 caption: Note: individuals 27 and 29 used CGM devices for less than one week.

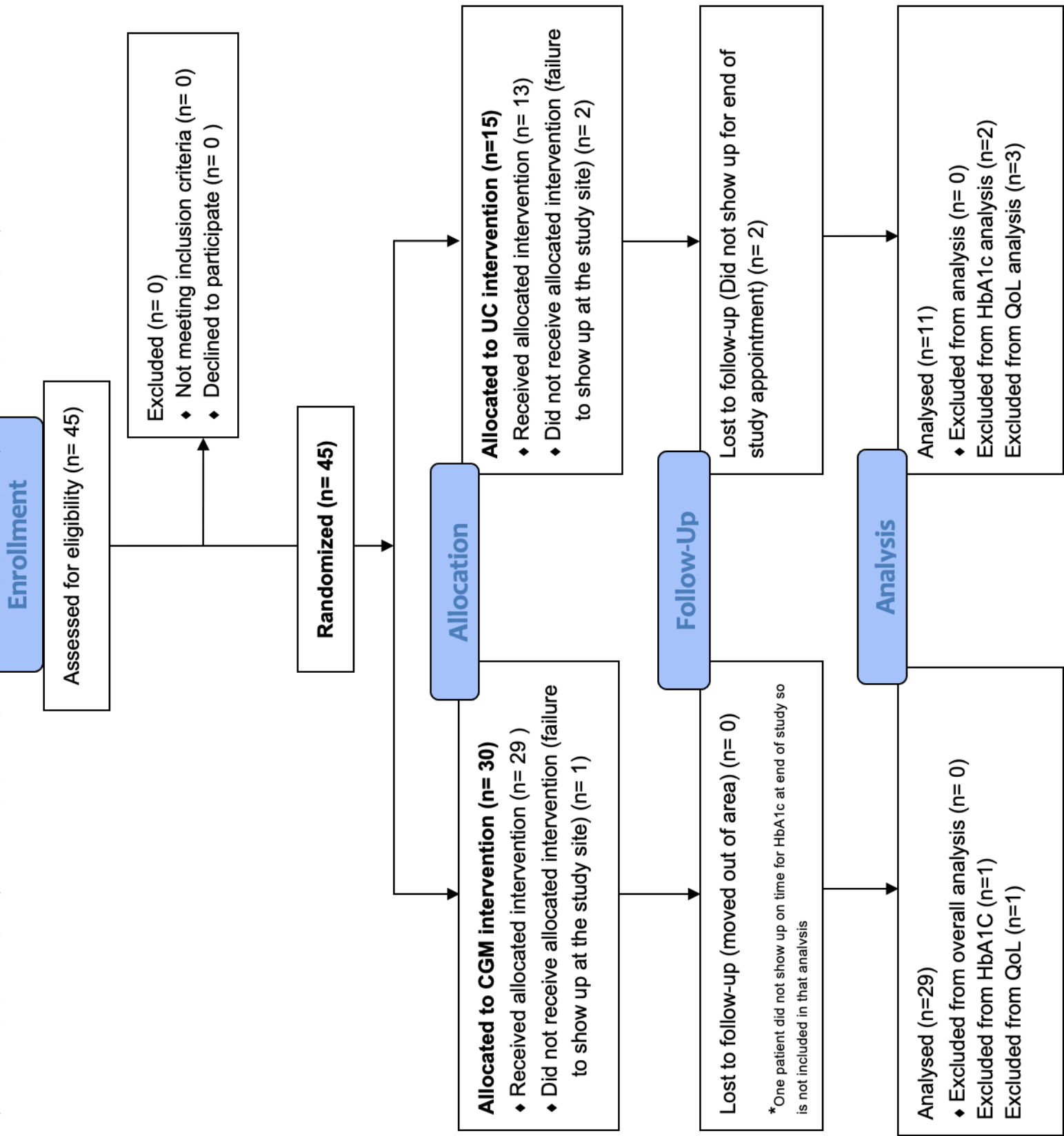
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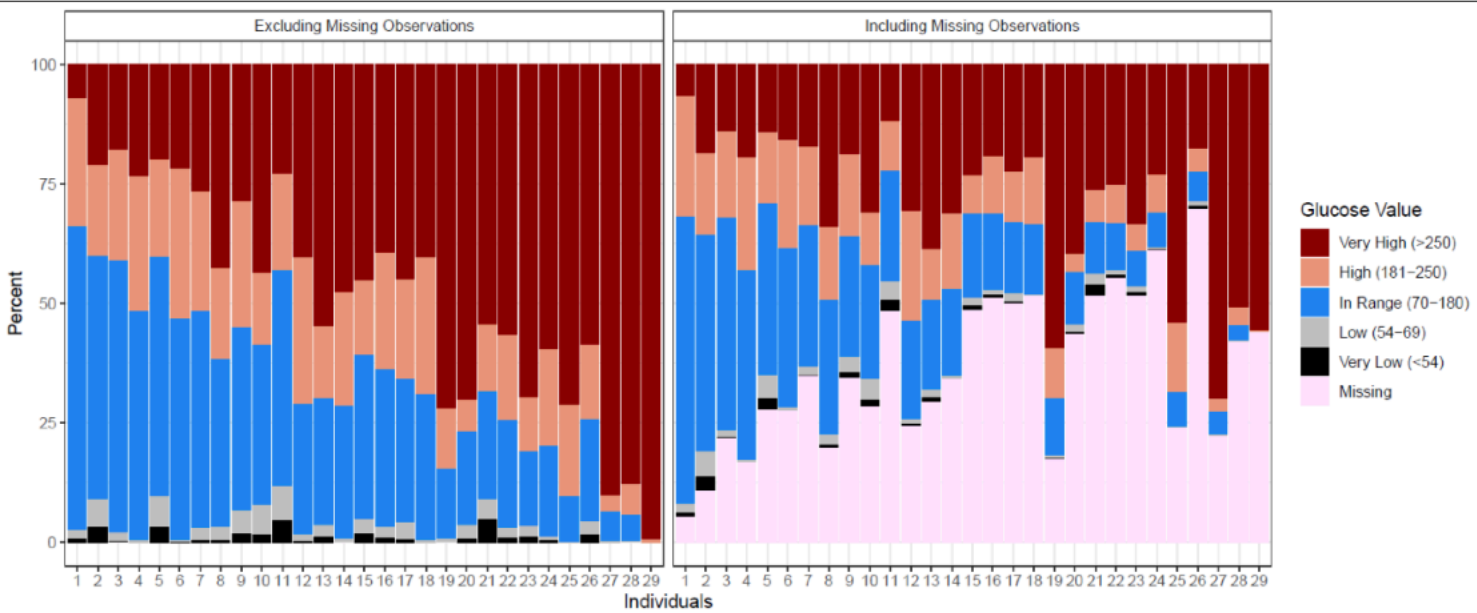
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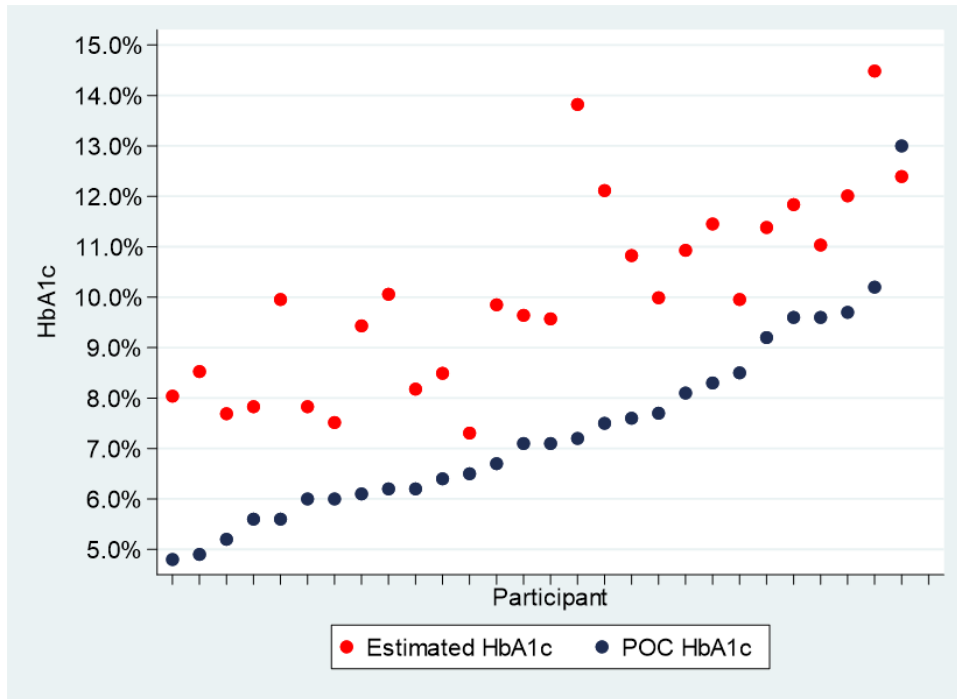
Supplementary Table 1: Quality of Life

	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			

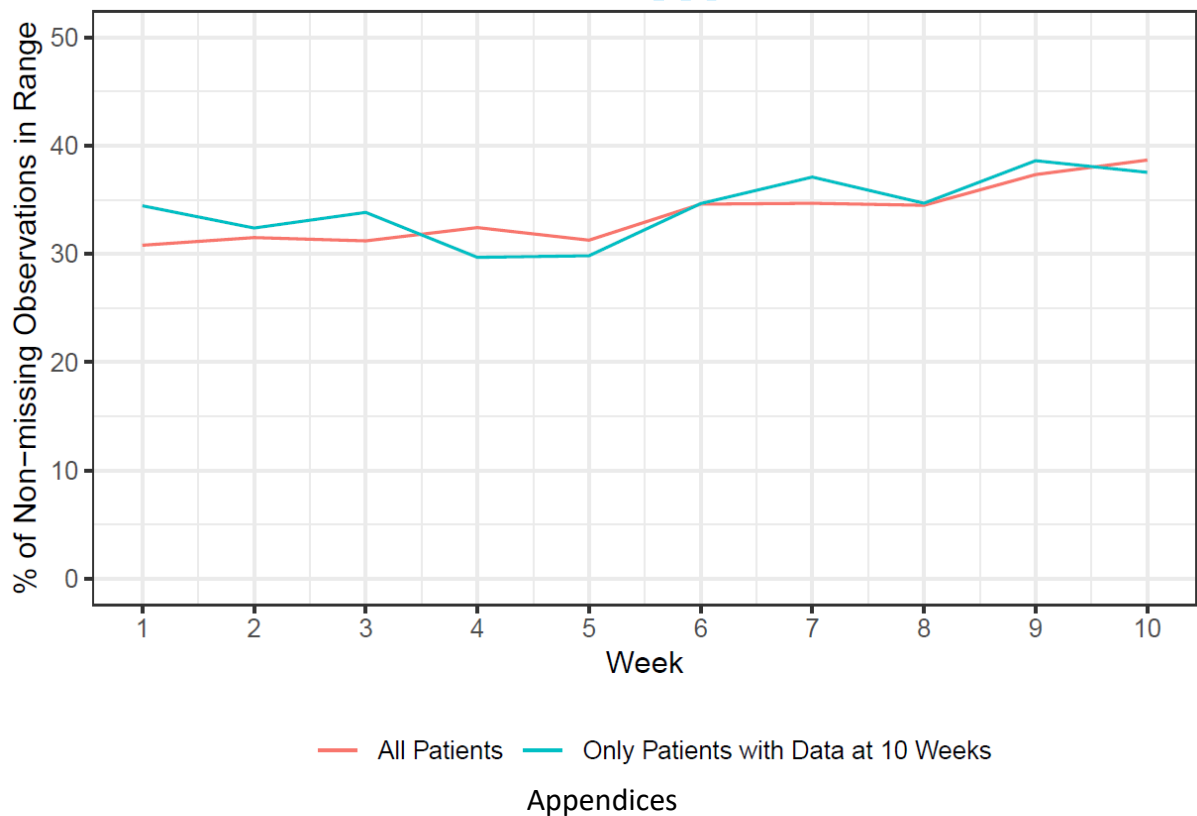
Note: There were 28 participants in the CGM arm and 10 in the usual care arm (1 and 3 of the original participants with no follow-up data in the respective arms). Coefficient, 95% CI, and p-value reported from longitudinal analysis of covariance, adjusted for baseline quality of life score, facility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

Dexcom G6
onetsetsani code ya sensor musanayambe kuika.

Kulika Sensor
Sakhani malo oyika pamimba (wazaka 2 ndi kupitilira apo) kapena m'mwamba mwamatako (zaka 2-17). Sakhani malo omwe mull mafuta. Pewani malo omwe muli mafupa, ziwengo, zojambula ndi malo oonekera.

1. Sambani ndi kuumsa manja. Pukutani malo a sensor ndi thonje la spirit.
2. Chotsani zomata mata. Osakhudza zomatira.
3. Iyani choikira pakhungu.
4. Chotsani kapamwamba ndi kudina batani.
5. 4. Chotsani choikira pakhungu
6. 6. Iyani choikira mujumbo ndi bweretsani kuchipadala, musataye.
7. Pukutani transmitter ndi thonje la spirit.
8. Iyani transmitter m'malo mwake.
9. Modekha dinikizani transmitter ndipo mumve kulira.
10. Sisitani modinikiza katatu m'mbali mwa chomatira sensor.

Pakatha masiko 10. Chotsani transmitter.

11. Matulani kansalu m'mbalimbali mwa sensor.
12. Pidani ndi kuthyola topanila kuti muchotse transmitter.
13. Chotsani transmitter.
14. Musataye transmitter. Mutha kugwiritsa ntchito kapena Bweretsani ku chipatala.

Credits for Translation: Dester Nakotwa (NCD Nurse, Neno).

Unblinded CGM Patient Handout **DEXCOM G6 PRO**

Patient downloads G6 app on their smart phone to view Dexcom G6 Pro Continuous Glucose Monitoring System (G6 Pro) readings.

Healthcare professional: Insert sensor (Section A) and attach transmitter (Section B). Complete sections C and D. Review this handout with patient, then give to them to take home.

A. Insert Sensor

1. Gather materials: applicator, transmitter, and wipes.
2. Pick sensor site. Avoid bones, muscle, irritated skin, tattoos, areas that get bumped.
3. Clean sensor site with alcohol wipe.
4. Peel off adhesive backing.
5. Place adhesive on skin.
6. Fold and break off safety guard.
7. Press button to insert sensor.
8. Discard applicator. (Follow local guidelines)

B. Attach Transmitter

1. Clean transmitter. Only use alcohol wipe.
2. Insert transmitter: tab first, into holder.
3. Click transmitter into place. Flush with holder.
4. Rub around patch 3 times.

C. Information patient needs for G6 app setup

1. Patient enters alerts settings in app.
Low Alert: _____ mg/dL
60 mg/dL-100 mg/dL
High Alert: _____ mg/dL
120 mg/dL-400 mg/dL
2. Patient enters transmitter SN in app.
PUT STICKER HERE
Don't give transmitter SN to blinded patient

D. Transmitter removal date **Return transmitter**

In person Other

Date _____
Time _____

G6 Pro Overview

G6 Pro takes your glucose reading every 5 minutes for 10 days. After returning the system, your healthcare professional reviews your glucose history and may adjust your medication, diet, or exercise.

Sensor (Measures glucose below skin)

Transmitter (Gives sensor readings)

What do I do?

- Keep your smartphone within 20 ft
- Shower and swim as normal
- Return to your healthcare professional as instructed

What don't I do?

- No MRI's
- No full-body scanners
- No sunscreen or lotions on transmitter
- No system parts in mouth, it's a choking hazard
- Don't remove transmitter, it'll end your sensor session

Continued on reverse

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

<p>Participant Training at Baseline (For both groups): One session of general diabetes education and management</p> <ul style="list-style-type: none"> • Glucose targets • Insulin dosing techniques and principles <ul style="list-style-type: none"> – 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.
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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

For peer review only



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:	<i>BMJ Open</i>
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 &

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	ENDOCRINOLOGY, International health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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5 2 **Randomized control trial for the feasibility of continuous glucose monitoring in patients**
6 3 **with type 1 diabetes at two district hospitals in Neno, Malawi.**
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10 7 Apoorva Gumber^{1*}, Francis Valeta^{2*}, Matthew M Coates¹, Celina Trujillo^{1,3,5}, Gina Ferrari^{1,3},
11 8 Medson Boti², Kenwood Kumwenda², Bright Mailosi², Dester Nakotwa², Laura Drown¹, Emily
12 9 Wroe^{1,3}, Ada Thapa¹, Victor Mithi², Beatrice Matanje², Amos Msekandiana^{6,7}, Paul H Park¹,
13 10 Chiyembekezo Kachimanga², Gene Bukhman^{1,3,4†}, Todd Ruderman^{2†}, Alma J Adler^{1†}
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2
3 46 **ABSTRACT**
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5 48 **Objectives:** To assess the feasibility and change in clinical outcomes associated with
6 49 Continuous Glucose Monitoring (CGM) use among a rural population in Malawi living with
7 50 type 1 diabetes **Design:** a 2:1 open randomized controlled feasibility trial

8 51 **Setting:** Two Partners In Health-supported Ministry of Health-run first level district hospitals
9 52 in Neno, Malawi

10 53 **Participants:** 45 people living with type 1 diabetes

11 54 **Interventions:** Participants were randomly assigned to Dexcom G6 CGM (n=30) use or usual
12 55 care (UC) (n=15) consisting of Safe-Accu glucose monitors and strips. Both arms received
13 56 diabetes education.

14 57 **Outcomes:** Primary outcomes included fidelity, appropriateness, and severe adverse events.
15 58 Secondary outcomes included change in HbA1c, acceptability, time in range (CGM arm only)
16 59 standard deviation of HbA1c, and quality of life.

17 60 **Results:** Participants tolerated CGM well but were unable to change their own sensors
18 61 which resulted in increased clinic visits in the CGM arm. Despite the hot climate, skin rashes
19 62 were uncommon but cut-out tape overpatches were needed to secure the sensors in place.
20 63 Participants in the CGM arm had greater numbers of dose adjustments and lifestyle change
21 64 suggestions than those in the UC arm. Participants in the CGM arm wore their CGM on
22 65 average 63.8% of the time. Participants in the UC arm brought logbooks to clinic 75% of the
23 66 time. There were three hospitalizations all in the CGM arm, but none were related to the
24 67 intervention.

25 68 **Conclusions:** This is the first RCT conducted on CGM in a rural region of a low-income
26 69 country (LIC). CGM was feasible and appropriate among PLWT1D and providers, but
27 70 inability of participants to change their own sensors is a challenge.

28 71 **Trial registration:** Trial registration number PACTR202102832069874. This study was
29 72 approved by National Health Sciences Research Committee of Malawi (IRB Number
30 73 IR800003905) and the Mass General Brigham (IRB number 2019P003554). The protocol was
31 74 previously published.
32 75

33 76 **Strengths and limitations of this study:**
34 77

- 35 78 1. Randomized controlled trial evaluating feasibility and acceptability of CGM in a rural,
36 79 low-literacy population in a low-income country
37 80 2. Study participants were followed for a period of 90 days, allowing for longitudinal data
38 81 on impact of CGM
39 82 3. Limited by small sample size
40 83
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44 87 **Keywords:** Type 1 diabetes, Continuous glucose monitoring (CGM), Self-monitoring,
45 88 technology, feasibility study, RCT, Low income countries.
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89 INTRODUCTION

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

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

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

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

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3 118 but not a complete picture, and neither provide real-time alerts about hypo- or
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5 119 hyperglycemia. The uptake of CGM devices in many high-income countries (HICs) is gradually
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7 120 increasing, with good acceptability and clinical outcomes. A recent international consensus
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9 121 statement on the use of CGM technology concluded that CGM data should be used for
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11 122 therapeutic treatment decisions related to hypoglycemia and glucose variability (12).

12
13 123 Currently, no data exist on the feasibility and effect on clinical outcomes of CGM for PLWT1D
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15 124 in rural areas of LICs especially in areas without electricity, and having low literacy and
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17 125 numeracy. To address this lack of evidence, we conducted a randomized trial to evaluate the
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19 126 feasibility of CGM technology and change in clinical outcomes among PLWT1D with limited
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21 127 literacy receiving diabetes care at two district hospitals in rural Malawi. Here we report
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23 128 quantitative results. While the qualitative results are important to understanding the
24
25 129 feasibility of CGM in this setting, we report them in a separate paper to provide greater
26
27 130 opportunity for discussion of themes and quotes (13). This study is approved by National
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29 131 Health Sciences Research Committee of Malawi (IRB Number IR800003905) and the Mass
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31 132 General Brigham (IRB number 2019P003554). The protocol was previously published(14).

32 33 133 **OBJECTIVES**

34
35 134 The objectives of this study are to (1) assess the feasibility and appropriateness of CGM use
36
37 135 among a rural population of PLWT1D and limited literacy in an LIC; (2) to determine if CGM
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39 136 use can have an effect on diabetes clinical outcomes among PLWT1D in rural regions of LICs
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41 137 and (3) determine the standard deviation of HbA1c across individuals at baseline to inform
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43 138 further studies.

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45 46 140 **METHODS**

47 48 141 **Study setting**

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50 142 The study was conducted at two rural Ministry of Health (MOH) supported first-level hospitals
51
52 143 in Neno district, Malawi, with a population of about 138,000(15), primarily relying on
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54 144 subsistence agriculture. Neno District Hospital is in a mountainous region near the
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56 145 Mozambique border and Lisungwi Community Hospital is in the lower, drier area near the
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58 146 Shire River. Both hospitals are similar in protocol and resources and are overseen by the same
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60 147 district leadership. Since 2007, Partners In Health (PIH), a US-based non-government

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3 148 organization known locally as Abwenzi Pa Za Umoyo (APZU), has partnered with MOH to
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5 149 improve healthcare and socioeconomic development in Neno District. In 2018, two advanced
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7 150 non-communicable disease (NCD) clinics providing high-quality care for complex NCDs,
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9 151 consistent with the Package of essential medicines for noncommunicable diseases-Plus (PEN-
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11 152 Plus) opened at Upper Neno and Lisungwi(16-18). Patients with T1D enrolled in this clinic
12
13 153 receive care from mid-level providers with specialized non-communicable disease (NCD)
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15 154 training. All insulin, syringes, and tools for SMBG are provided free of charge to all patients at
16
17 155 their routine monthly appointments. PLWT1D typically use human insulin, intermediate-
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19 156 acting (NPH) two times daily and fast- acting (regular) two to three times daily. Every
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21 157 household in Neno is visited by a community health worker (CHW) monthly for education and
22
23 158 screening for multiple common conditions, enrolment into maternal and chronic care, and
24
25 159 accompaniment to the clinic(19).
26

27 161 **Study Participants**

28
29 162 Eligibility criteria for this study included a clinical diagnosis of T1D in PLWT1D, in diabetes care
30
31 163 for at least one year, and seeking care at either of the PIH-supported MOH hospitals. We did
32
33 164 not exclude anyone based on age. Exclusion criteria included pregnancy, mental impairment,
34
35 165 and the inability of the subject or care provider to use a CGM device. Figure 1 shows the flow
36
37 166 diagram of the recruitment process.
38

39
40 168 Each participant was required to complete an informed consent/ assent (children <18 years
41
42 169 of age) form on the day of the enrolment. Study staff were trained to assist patients with
43
44 170 limited literacy with the consent process.
45

46 171

47 172 **Design**

49 173 **Randomization**

50
51
52 174 All 45 participants known to have T1D and seeking care at hospitals in Neno met the study
53
54 175 criteria and were approached for willingness to participate in this study. All agreed and were
55
56 176 randomly assigned via a random numbers table to either of the two arms: CGM (Dexcom G6,
57
58 177 Dexcom, Inc.) arm and usual care arm (using blood glucose meter) in a 2:1 ratio. Study
59
60

1
2
3 178 investigators and personnel were masked to the randomization sequence which was created
4
5 179 by a senior researcher.
6

7 180

8 181 Provider training

9 182 Clinical providers were required to complete one month of virtual training on routine diabetes
10
11 183 care and understanding CGM in the management of diabetes performed by the study team
12
13 184 (including two nurse practitioners and two clinical officers trained in T1D care). Then,
14
15 185 providers completed a two-week in-person hands-on training where they were required to
16
17 186 wear a CGM and learn how to use Clarity (Dexcom CGM software). Providers were trained to
18
19 187 review data from CGM downloads and SMBG logbook data and make individualized dose
20
21 188 adjustments, changes in alarm alerts on the CGM reader, and recommendations for lifestyle
22
23 189 and insulin dosing as per usual practice. Clear protocols warranting medical attention were
24
25 190 supplied to the providers, and any reported adverse events were immediately assessed and
26
27 191 documented. Provider training focused on: glucose targets; goal of time in range (TIR), insulin
28
29 192 dosing techniques and principles; basics of insulin therapy and meal planning; understanding
30
31 193 signs and strategies for managing hypoglycemia and hyperglycemia; understanding sick day
32
33 194 management; understanding food insecurity and insulin dose adjustments; and
34
35 195 troubleshooting common problems with Dexcom devices.
36

37 196

38 197 Intervention

39 198 Participants in the CGM arm were provided with a transmitter, a receiver, and sensors
40
41 199 (Dexcom G6) inserted under the skin using an applicator to wear real-time continuous
42
43 200 glucose monitoring technology for three months. All CGM equipment was provided free by
44
45 201 Dexcom. Each transmitter had a shelf life of 90 days and each sensor had a shelf life of 10
46
47 202 days after which a new sensor needs to be applied. Participants in the CGM arm were
48
49 203 instructed to use CGM daily and were advised to either change the sensor on their own or
50
51 204 follow up after ten days for new sensor insertion. Individualized clinical recommendations
52
53 205 were made by their providers at each visit using standardized material developed for the
54
55 206 study based on Dexcom training materials (Appendix A). Participants in the CGM arm
56
57 207 received a Chichewa-language handout at the beginning of the study to educate them about
58
59 208 the features of CGM and readings obtained from the reader.
60

209

210 *Comparator*

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

216

217 *Both Arms*

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

225

226 **Data collection and interviews**

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

235

236

237 **Outcomes**

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

1
2
3 240 have negative effects on clinical outcomes for users. For that reason we include two clinical
4
5 241 outcomes, HbA1c and time in range. Primary outcomes were split into implementation
6
7 242 outcomes, defined using the Proctor (21) framework, and clinical outcomes.
8

9 243

10 244 Implementation outcomes

11 245 *Fidelity*

12 246 Fidelity is defined here using variables reflecting patients' adherence to the technology used
13
14 247 (21). In the CGM arm, fidelity was defined by number of sensors worn, the percent of time
15
16 248 sensors were worn (based on Clarity reports), and times that dose or lifestyle adjustments
17
18 249 were made. In the usual care arm, fidelity was defined as the percent of expected blood
19
20 250 glucose readings logged, the percent of participants who brought logbooks to the clinic
21
22 251 during the study period, percent of expected times blood glucose test was performed, the
23
24 252 number of times insulin adjustments were made, and how often lifestyle adjustments were
25
26 253 suggested.
27

28 254

29 255 *Appropriateness*

30 256 Appropriateness was defined as the perceived fit and relevance or compatibility of
31
32 257 CGM(21). This was based on sensor problems, reporting of technological issues, and
33
34 258 qualitative interviews.
35

36 259

37 260 Clinical outcomes

38 261

39 262 *Severe adverse events*

40 263 Severe adverse events were measured from patient self-reports, CGM or home glucose
41
42 264 meters, or clinician reports.
43

44 265

45 266 Secondary outcomes

46 267 *Implementation outcomes*

47 268 Acceptability was defined using Proctor's framework as the perception that CGM was
48
49 269 agreeable, palatable, or satisfactory (21). This was measured through qualitative interviews
50
51 270 with PLWT1D and providers.
52
53
54
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271

272 *Clinical outcomes*

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

278

279 *Change in HbA1c*

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

285

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

291

292 **Statistical methods**

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

302

303 HbA1c analysis

304 To test whether the change in HbA1c differed between the CGM and usual care arms, we
305 used the linear regression model specified below, equivalent to longitudinal analysis of
306 covariance, where HbA1c at follow-up ($HbA1c_{t1}$) is predicted by study arm (SA), HbA1c at
307 baseline ($HbA1c_{t0}$), facility site (Site), age (Age), female gender (Fem), diagnosis year (DY),
308 and body mass index (BMI), with an error term, ε , assumed normally distributed. The
309 coefficient on study arm, β_1 , was the parameter of interest.

$$310 \quad HbA1c_{t1} = \beta_0 + SA\beta_1 + HbA1c_{t0}\beta_2 + Site\beta_3 + Age\beta_4 + Fem\beta_5 + DY\beta_6 + BMI\beta_7 + \varepsilon$$

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

314

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

320

321 Quality of life analysis

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

328

329 Percent of time worn and time in range analyses

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

1
2
3 333 observation was present for a period longer than 5.06 minutes, we considered each five-
4
5 334 minute increment between the previous and subsequent observations as missing. Then, we
6
7 335 calculated the proportion of all observations that were missing. We calculated the
8
9 336 proportion of non-missing observations within the desired blood glucose range (70 to 180
10
11 337 mg/dL) to estimate time in range, as well as the proportion that were very low (under 54
12
13 338 mg/dL), low (54 mg/dL to 69 mg/dL), high (181 mg/dL -250 mg/dL), and very high (over 250
14
15 339 mg/dL). We additionally calculated the mean and interquartile range of the non-missing
16
17 340 observations.

18 341

19
20 342 The CGM sensors lasted 10 days, but many patients returned to the clinic every 14 days to
21
22 343 obtain replacement sensors. Therefore, a substantial proportion of the missingness was
23
24 344 related to timing of sensor replacement. We estimated this proportion by assuming that any
25
26 345 missingness on the day of a sensor replacement (recorded by study clinicians) was related to
27
28 346 the replacement, and any missingness contiguous with (i.e., no non-missing observations
29
30 347 between) and prior to (including in previous days) that period of missingness was
31
32 348 categorized as related to the sensor replacement. We then tabulated the proportion of
33
34 349 missing observations related to sensor replacement. Not all individuals experienced long
35
36 350 periods missing a sensor, as some felt comfortable replacing sensors at home and were
37
38 351 given extra sensors by study staff.

39 352

40 353 **Qualitative methods**

41
42 354 We conducted a series of semi-structured interviews with 10 patients (five in each arm) at the
43
44 355 beginning and end of the study. We also interviewed five providers (two nurses and three
45
46 356 clinicians) who provided care to the patients during the study period. Trained members of the
47
48 357 study team conducted all interviews. Provider interviews were conducted in English. Patient
49
50 358 interviews were conducted in Chichewa, and translated by a bilingual researcher. All
51
52 359 interviews were audio recorded and transcribed by a trained researcher. Interviews were
53
54 360 coded in Dedoose and analyzed using a thematic framework using a-priori themes.

55 361

56 362 **Deviations from protocol**

1
2
3 363 We initially planned a two-day training for participants, with one day devoted to
4
5 364 comprehensive T1D education. However, due to long distances needed to travel for
6
7 365 participants and resulting missed school and work, two consecutive days was not feasible.
8
9 366 Instead, for two months before the start of the study, providers gave enhanced diabetes
10
11 367 education to all participants. In the protocol outcomes, we had stated the percent of expected
12
13 368 times CGM and SMBG information was used to inform lifestyle-adjusted interventions, and
14
15 369 we were unable to determine the percent so we used number of times instead. We had
16
17 370 initially included change in HbA1c as a primary outcome, but due to lack of power we changed
18
19 371 this to a secondary outcome.
20
21 372

22 373 **Patient and public involvement**

23 374 PLWT1D were engaged throughout the study. Three of the outcomes of this research were
24
25 375 feasibility, acceptability, and appropriateness, so much of the study involved gaining
26
27 376 perspectives, experiences and views of the technology by PLWT1D. Two of the study
28
29 377 coauthors (GF & AG) are living with T1D, and were involved throughout the design of the
30
31 378 protocol, tools, training and implementation of the study.
32
33 379

34 380 **RESULTS**

35 381 **Participants**

36 382 There were 45 individuals with T1D meeting the inclusion criteria at the two eligible
37
38 383 hospitals. When approached by phone, all agreed to be included and were randomized, 30
39
40 384 to the CGM arm and 15 to the UC arm. On the day of trial initiation, one from the CGM arm
41
42 385 and two from the UC arm did not present and therefore did not participate. At the end of
43
44 386 the study, one participant in the CGM arm and two from the UC arm were not present for
45
46 387 their final evaluations and were considered lost to follow-up (Figure 1). The trial was
47
48 388 initiated on April 11th 2022 in Lisungwi district hospital and April 14th 2022 in Upper Neno
49
50 389 district hospital and ran for 90 days. Table 1 shows baseline characteristics of trial
51
52 390 participants in both arms.
53
54 391

55 392 Table 1: Characteristics of participants at baseline

	Study arm	All
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	<i>CGM</i> (N=29)	<i>Usual care</i> (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

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

414

415 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
<i>CGM arm</i>		
Sensors worn, mean (range)	6.8 (2,9)	
Percent of time worn, mean (SD)	63.8 (16.1)	
<i>Usual care arm</i>		
Consultations with logbook brought to clinic (%)	75.0	
Readings logged (%)	51.3	

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

417

418 In the usual care arm, participants brought logbooks to consultations 75% of the time.

419 However, readings in logbooks corresponded to glucose meters readings only 51.3% of the
420 time.

421

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

427

428 *Appropriateness*

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

1
2
3 432 Clinicians reported that after multiple CGM insertions, patients felt confident with the
4 application process and were able to self-apply with guidance, however they were unable to
5 433
6 correctly input the sensor codes. In total, there were 28 cases of sensor failure over the
7 434
8 three-month trial period. During the first sensor use, three individuals complained of
9 435
10 discomfort but worked with providers to find a more comfortable way of wearing them. In
11 436
12 the first month, three participants accidentally removed the sensors, but there were no
13 437
14 reported cases after the first month. Rashes and skin irritation were not a commonly
15 438
16 encountered complaint in the CGM arm. The hot weather caused a few participants
17 439
18 difficulty with keeping the sensor attached. We overcame this using skin Tac adhesive and
19 440
20 cut-out tape overpatches to secure the sensors in place and prevent removal. No sensor
21 441
22 related bleeding or potential skin reaction around or under the sensor was observed. There
23 442
24 were no reported problems with the solar chargers, and participants were able to use the
25 443
26 solar chargers for light in their houses.
27 444
28

445

446 Clinical outcomes

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

451

452 Mean endline point-of-care HbA1c was 7.4% (95% CI 6.6%, 8.1%). Mean estimated HbA1c
453 was significantly higher, at 10.1% (95% CI 9.3%, 10.8%) and mean difference of 2.7% (95% CI
454 2.2%, 3.2%; $p < 0.05$). Supplementary Figure 1 shows point-of-care HbA1c and estimated
455 HbA1c for each participant in the CGM arm.

456

457 **Secondary Outcomes**

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

462

1
2
3 463 The average percent TIR in recorded readings (not including missing data) was 30.6% (SD
4 464 16.1%) (Figure 2). Among the 27 CGM arm participants with more than one week of
5 465 recorded data, the average TIR was 32.6% (SD 14.7%). Over the course of the study, there
6 466 was an increase in the time in the range starting in week 6 (Supplementary Figure 2). The
7 467 average time in range was 30.8% in week 1, and 38.7% in week 10. To examine whether this
8 468 increase in TIR was due to drop off of non-compliant participants, we conducted a sensitivity
9 469 analysis looking at only participants who we had data for at 10 weeks. Among the 20
10 470 participants with greater than 5% non-missing data in week 10, the average time in range in
11 471 week 1 was 34.5%, and the average in week 10 was 37.5% (Supplementary Figure 2).
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22 473 After three months, we observed an increase of 0.2 percentage points in HbA1c in the usual
23 474 care arm (N= 11 as follow-up HbA1cs missing for two participants) and a reduction of 1.2
24 475 percentage points in the CGM arm (N=28) compared to baseline. After adjusting for baseline
25 476 HbA1c levels and other covariates, participation in CGM compared to usual care was
26 477 associated with a 1.1 percentage point lower HbA1c; confidence intervals were compatible
27 478 with a moderate to null reduction in the CGM arm relative to the usual care arm (95% CI: 2.4
28 479 percentage point reduction to 0.3 percentage point increase, Table 3).
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36 481 Pretrial, there was a standard deviation of 2.1 in HbA1c pooled across two arms, although
37 482 baseline HbA1c was low overall compared to what is generally expected in this type of
38 483 setting(24-26).
39
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41
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43

44 485 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

486 486 Model 1 adjusted for baseline HbA1c only; Model 2 adjusted for baseline HbA1c, facility site,
487 487 age, sex, diagnosis year, and BMI. Note: 28 of the original 29 were included from the CGM
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3 488 arm because 1 person did not have a follow-up HbA1c measurement, and 11 of 13 were
4 489 included in the usual care arm because of missing follow-up measures.

5 490 CGM: Continuous Glucose monitoring, CI: Confidence interval, SD: standard deviation

6 491

7
8
9 492 Over the course of the study, QoL (N=28 in CGM and N=10 in UC) was assessed using WHO-
10 493 BREF increased across all domains (Supplementary Table 1). Though unadjusted QoL
11
12 494 increased slightly more in the UC arm (9.0) than the CGM arm (6.7), confidence intervals for
13
14 495 differences in the change in QoL between groups were large, and we did not find any strong
15
16 496 evidence of differences.

17 497

18 498

19 499 **DISCUSSION**

20 500 **Summary of main results**

21
22
23 501 This is the first RCT to be carried out in a rural area of a LIC on the feasibility of CGM. While
24
25 502 participants wore their sensors just under two-thirds of the time, much of the missingness
26
27 503 (over 70% on average) was attributable to their inability to change their sensors. The most
28
29 504 pervasive barrier to CGM use among patients was the reported limited digital literacy and
30
31 505 confidence with the sensor application process, which required patients in the CGM arm to
32
33 506 come more frequently into the clinic than the usual care arm. However, with time and
34
35 507 multiple CGM insertions, patients felt confident with the application process and could self-
36
37 508 apply under the guidance of the clinicians, but still needed help with numerically entering
38
39 509 sensor codes to activate them. Skin rashes were not a notable complaint, although due to the
40
41 510 hot weather there was some difficulty with sensor adhesion that was rectified by using skin
42
43 511 Tac adhesive and cut-out tape overpatches to secure the sensors in place. After the first few
44
45 512 weeks, participants tolerated the CGM well, and clinicians were far more likely to make dose
46
47 513 adjustments in the CGM arm than the usual care arm. There was a trend towards greater
48
49 514 reduction in HbA1C in the CGM arm than in the usual care arm. However, there were many
50
51 515 more consultations in the CGM arm, so it is difficult to attribute the improvement to the CGM
52
53 516 or the greater number of consultations. Given the four-day lag between sensor end and
54
55 517 replacement, the reduction may have been greater without this lag. The intervention was
56
57 518 deemed acceptable by participants with the greatest complaint being around sensor beeping.

58 519

520 Comparisons with other studies

521 This is the first RCT conducted in a rural setting in a LIC to assess the feasibility of CGM and
522 its effect on clinical outcomes and quality of life among people living with T1D. To date,
523 there are less than a handful of studies on CGM use in the African continent, none of which
524 are randomized control trials. One of these studies evaluated the glycemic profile – glucose
525 exposure, variability, stability, and risk of hypoglycemia – of people living with T1D and T2D
526 in South Africa, across 16 different clinics(27). In Uganda, Niwaha and colleagues conducted
527 a study to assess the risk of hypoglycemia for people living with T2D being treated with
528 sulphonylureas or insulin and did not include PLWT1D(28). While the study in South Africa
529 mentioned that some sensors failed to record data, neither this study nor that of Niwaha
530 looked specifically at fidelity, appropriateness, or acceptability. A short observational study
531 by McClure Yauch and Velazquez (2020) was conducted at national referral hospitals in
532 urban areas in Kenya and Uganda to assess feasibility of CGM use and the glycemic profile of
533 children and young adults affected by T1D using CGM technology (29). They found the use
534 of this technology was tolerated by patients and expressed hope for wider use in the future.
535 This urban study reported an average HbA1c of 10.9% with a SD of 2.7 compared to our
536 average baseline HbA1c of 8.3% and endline HbA1c of 7.5% with a SD of 2.1. Their TIR was
537 31% compared to the TIR in our study of over 37% by week 10 (32.6% across the whole
538 study period among the 27 participants in the CGM arm with more a few days of data). All
539 three of these studies used the Freestyle Libre Pro, and users were blinded to their glucose
540 data and had CGM use of 14 days. In our study we used the Dexcom G6 CGM for 90 days,
541 which provides real-time glucose data to the user and can be used to make treatment
542 decisions. None of these studies examined any association between CGM use and QOL.

543
544 Comparison of endline point-of-care HbA1c to estimated HbA1c based on CGM values
545 showed that point-of-care HbA1c may be overestimating glycemic control–A few theories
546 for the discrepancy between HbA1c and mean blood glucose levels have been proposed,
547 including the presence of hemoglobinopathies, individual variations in the lifespan of red
548 blood cells, renal impairment, and nutritional deficiencies (e.g., iron-deficiency anemia,
549 Kwashiorkor, Marasmus) (30,31). No hemoglobinopathies are present in this patient
550 population. Additionally, numerous assays for point-of-care HbA1c testing have become

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2
3 551 available over the last decade of possibly varying quality. These findings reinforce that
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5 552 HbA1c alone may not be adequate to evaluate glycemic control in PLWT1D, adding to
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7 553 current literature highlighting the importance of availability for additional ways to evaluate
8
9 554 glycemic control, such as SMBG or CGM.

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11 555
12 556 Despite challenges participants experienced with changing sensors and data missingness,
13
14 557 the amount of glucose data recorded from sensor readings in this study - 63.8% of the time
15
16 558 (median: 65.5%, interquartile range: 49.9-75.6% sensitivity analysis is mean: 63.5%; median:
17
18 559 65.5%; IQR; 49.3-75.7%.) and 87% when excluding missingness due to lag in sensor change –
19
20 560 is higher than data from sensor readings [mean of 51.14 days (60.9%) ($SD = 20.86$), range
21
22 561 20–81 days] in a 90-day pre- and posttest pre-experimental study with children,
23
24 562 adolescents, and young adults with poorly controlled diabetes living in the U.S.(32). This
25
26 563 underscores the importance, benefits, and potential for high impact of ensuring access for
27
28 564 glucose monitoring devices for PLWT1D in low-resources settings.

29 565

30 566 **Limitations**

31
32 567 This was a feasibility trial with only 42 individuals, it was not powered for seeing differences
33
34 568 between study arms in outcomes like HbA1c and QoL. Due to the inability of patients in the
35
36 569 CGM arm to change their device sensor, many patients ended up seeing providers twice a
37
38 570 month compared to once a month in the usual care arm, making it difficult to separate
39
40 571 effects of technology versus the effect of the increased frequency of visits. Additionally,
41
42 572 providers were excited about the new technology and may have paid greater attention to
43
44 573 patients in the CGM arm. All participants in the study had a diagnosis of T1D, however,
45
46 574 limited resources and a lack of pancreatic antibody and C-peptide testing may mean some
47
48 575 patients were misdiagnosed. This study was conducted for three months. While this is far
49
50 576 longer than other studies, reduction in HbA1c levels and behavior change can take longer
51
52 577 than three months, so a longer study may have found greater effects. Conversely, we do not
53
54 578 know what adherence would look like after three months.

55 579

56 580 **Implications for future research and practice**

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2
3 581 Our study suggests that CGM is feasible, appropriate, and acceptable in rural Malawi, and
4
5 582 may show greater effectiveness in lowering HbA1c than SMBG. We highlight the need to
6
7 583 include practical digital literacy and numeracy training for patients when considering CGM
8
9 584 as a viable clinical option in diabetes management in such settings, and future studies and
10
11 585 practice should explore ways participants with low literacy can learn to change sensors
12
13 586 independently. Newer models of CGM (Dexcom G7, Freestyle Libre 2 and Freestyle Libre 3)
14
15 587 do not require sensor codes to be inputted for activation, so may be better suited to this
16
17 588 setting. As devices were donated by Dexcom, this study did not examine costs, but
18
19 589 continued global advocacy is necessary to ensure equitable access to intermediate T1D care
20
21 590 for PLWT1D in LICs. Other studies may examine if short periods of intensive CGM use are
22
23 591 equally effective as a training tool for both patients and providers allowing a more granular
24
25 592 assessment of glycemic control than previously possible with glucose meters. In contrast,
26
27 593 other studies looking at longer lengths of time using CGM may be able to explore if this is a
28
29 594 tool that can enhance PLWT1D's understanding of their condition, improve diabetes self-
30
31 595 management, decrease adverse events and diabetes-related complications, advance
32
33 596 providers' skills and knowledge, and assist with decision-making around insulin initiation for
34
35 597 people living with type 2 diabetes. Further, examining if there is added benefit and cost
36
37 598 effectiveness of real-time CGM compared to flash glucose monitoring and un-blinded CGM
38
39 599 compared to blinded in this setting is warranted.

600

601 **CONCLUSION**

602 This is the first RCT conducted on CGM in a rural region of a LIC. Overall, this small
603
604 feasibility study conducted in one Malawian district found CGM to be feasible and
605
606 appropriate among PLWT1D and their health care providers. Inability of participants to
607
608 change their own sensor is the biggest challenge, though could be addressed with use of
609
610 newer sensor models. Although not statistically significant, the downward trend in HbA1c in
611
612 study arm is promising and worth investigating over a longer period, especially in light of
613
614 increased TIR from baseline to endline. The current model of care needs to be strengthened
615
616 and TIR continues to be low — posing higher risk for acute and chronic complications among
617
618 this population.

611

1
2
3 612 **ACKNOWLEDGMENTS**
4

5 613 Roy Beck for advice on trial design.
6

7 614

8
9 615 **CONTRIBUTIONS**

10 616 Study and tool design: AJA, TR, FV, CT, GF, AM, EW, CK, GB, PP.

11 617 Training: AG, CT, GF
12

13 618 Data analysis: MMC, FV, AG, AJA, AT, LD
14

15 619 All authors contributed to the final manuscript
16

17 620 GB, TR, and AJA share senior authorship.
18

19 621
20

21 622 **COMPETING INTERESTS**
22

23 623 The authors have no competing interests.
24

25 624

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29

30 627 number 2105-04638. Dexcom generously donated CGM Dexcom 6 glucose meters and
31

32 628 sensors for the study free of charge.
33

34 629

35 630 **DATA AVAILABILITY STATEMENT**
36

37 631 De-identified data are available upon reasonable request from the corresponding author
38

39 632 (AJA) at aadler2@bwh.harvard.edu.
40

41 633
42

43 634 **FIGURES LEGEND**
44

45 635 Figure 1: Consort study flow diagram

46 636 Figure 2: Time in range for each participant with missing data included and not included
47

48 637 Figure 2 caption: Note: individuals 27 and 29 used CGM devices for less than one week.
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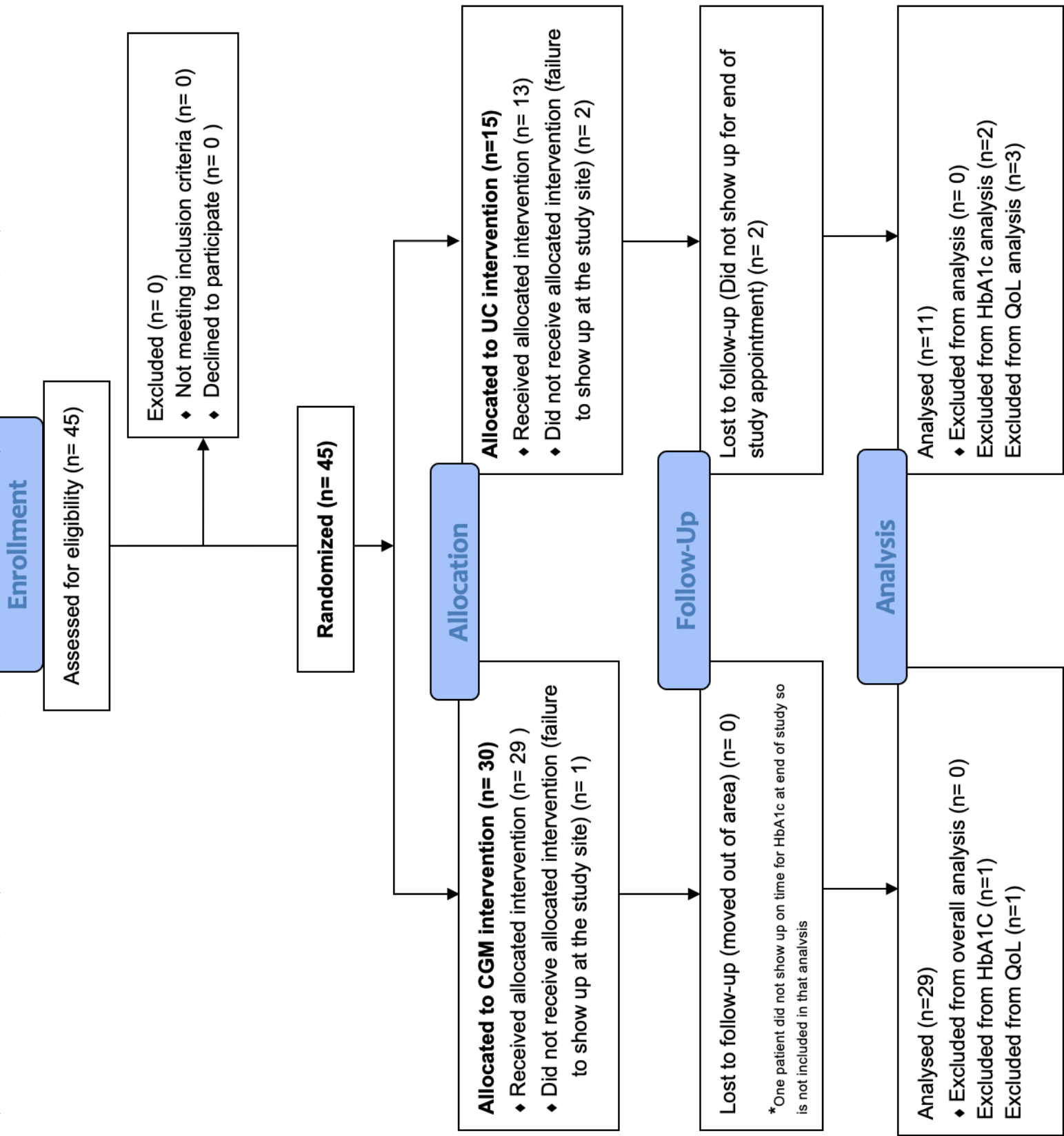
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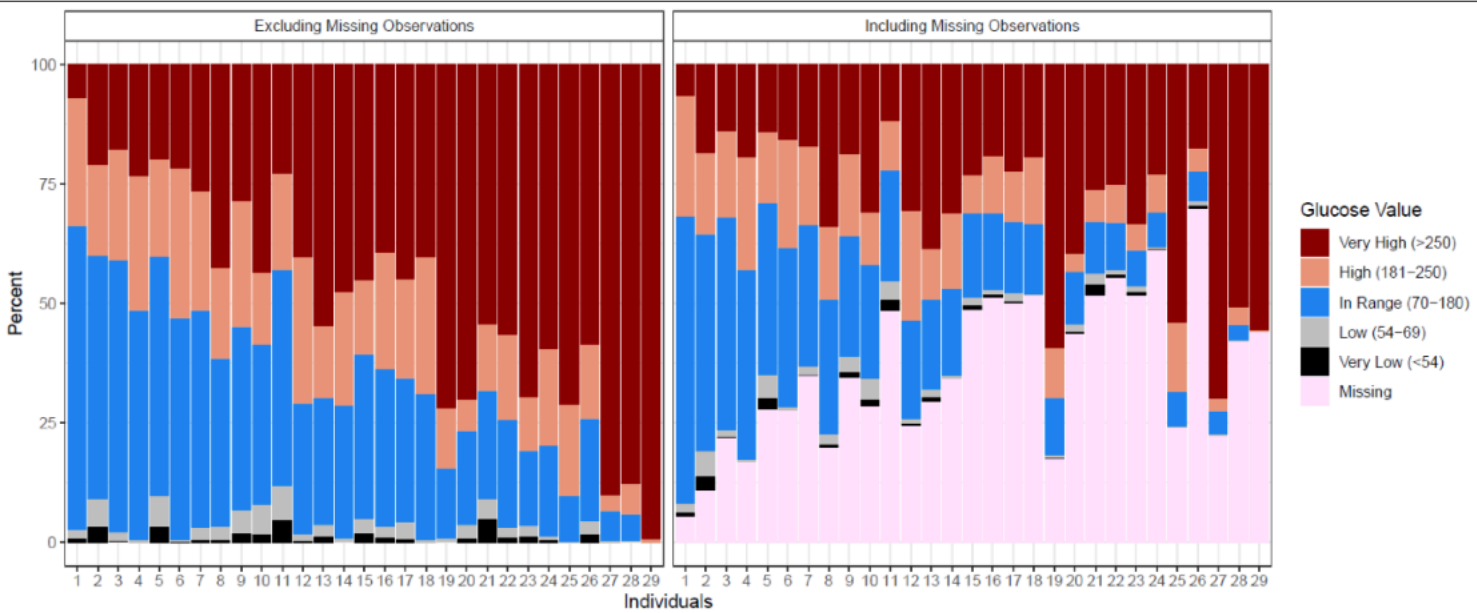
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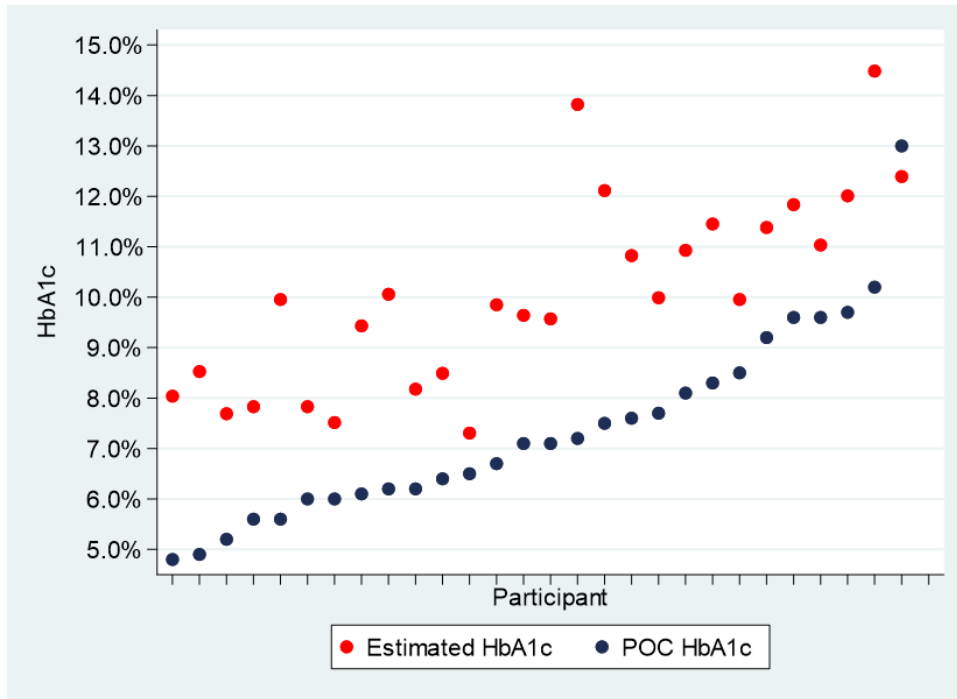
Supplementary Table 1: Quality of Life

	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			

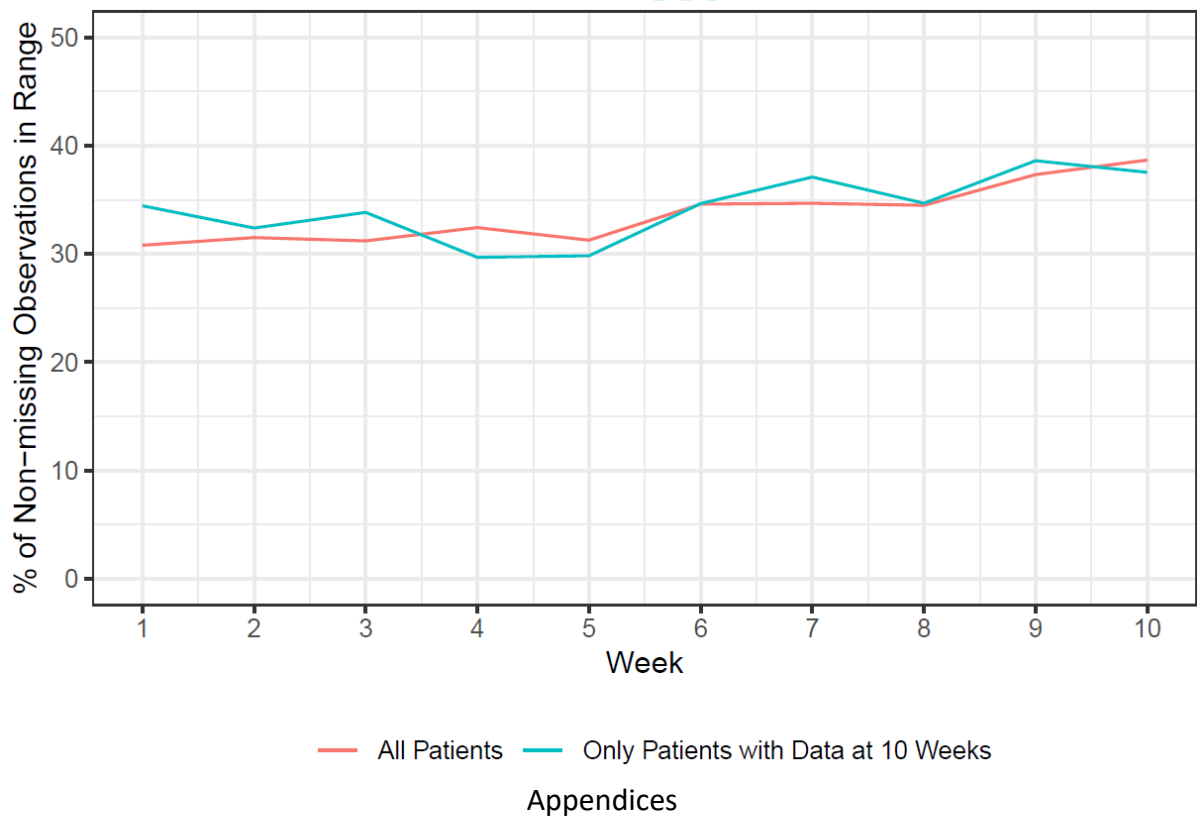
Note: There were 28 participants in the CGM arm and 10 in the usual care arm (1 and 3 of the original participants with no follow-up data in the respective arms). Coefficient, 95% CI, and p-value reported from longitudinal analysis of covariance, adjusted for baseline quality of life score, facility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

Dexcom G6
onetsetsani code ya sensor musanayambe kuika.

Kulika Sensor
Sakhani malo oyika pamimba (wazaka 2 ndi kupitilira apo) kapena m'mwamba mwamatako (zaka 2-17). Sakhani malo omwe mull mafuta. Pewanu malo omwe muli mafupa, ziwengo, zojambula ndi malo oonekera.

1. Sambani ndi kuumsa manja. Pukutani malo a sensor ndi thonje la spirit.
2. Chotsani zomata mata. Osakhudza zomatira.
3. Iyani choikira pakungu.
4. Chotsani kapamwamba ndi kudina batani.
5. 4. Chotsani choikira pakungu.
6. 6. Iyani choikira mujumbo ndi bweretsani kuchipadala, musataye.
7. Pukutani transmitter ndi thonje la spirit.
8. Iyani transmitter m'malo mwake.
9. Modekha dinikizani transmitter ndipo mumve kulira.
10. Sisitani modinikiza katatu m'mbali mwa chomatira sensor.

Pakatha masiko 10. Chotsani transmitter.

11. Matulani kansalu m'mbalimbali mwa sensor.
12. Pidani ndi kuthyola topanila kuti muchotse transmitter.
13. Chotsani transmitter.
14. Musataye transmitter. Mutha kugwiritsa ntchito kapena Bweretsani ku chipatala.

Credits for Translation: Dester Nakotwa (NCD Nurse, Neno).

Unblinded CGM Patient Handout **DEXCOM G6 PRO**

Patient downloads G6 app on their smart phone to view Dexcom G6 Pro Continuous Glucose Monitoring System (G6 Pro) readings.

Healthcare professional: Insert sensor (Section A) and attach transmitter (Section B). Complete sections C and D. Review this handout with patient, then give to them to take home.

A. Insert Sensor

1. Gather materials: applicator, transmitter, and wipes.
2. Pick sensor site. Avoid bones, muscle, irritated skin, tattoos, areas that get bumped.
3. Clean sensor site with alcohol wipe.
4. Peel off adhesive backing.
5. Place adhesive on skin.
6. Fold and break off safety guard.
7. Press button to insert sensor.
8. Discard applicator. (Follow local guidelines)

B. Attach Transmitter

1. Clean transmitter. Only use alcohol wipe.
2. Insert transmitter: tab first, into holder.
3. Click transmitter into place. Flush with holder.
4. Rub around patch 3 times.

C. Information patient needs for G6 app setup

1. Patient enters alerts settings in app.
Low Alert: _____ mg/dL
60 mg/dL-100 mg/dL
High Alert: _____ mg/dL
120 mg/dL-400 mg/dL
2. Patient enters transmitter SN in app.
PUT STICKER HERE
Don't give transmitter SN to blinded patient

D. Transmitter removal date **Return transmitter**

In person Other

Date _____
Time _____

G6 Pro Overview

G6 Pro takes your glucose reading every 5 minutes for 10 days. After returning the system, your healthcare professional reviews your glucose history and may adjust your medication, diet, or exercise.

Sensor (Measures glucose below skin)

Transmitter (Gives sensor readings)

What do I do?

- Keep your smartphone within 20 ft
- Shower and swim as normal
- Return to your healthcare professional as instructed

What don't I do?

- No MRI's
- No full-body scanners
- No sunscreen or lotions on transmitter
- No system parts in mouth, it's a choking hazard
- Don't remove transmitter, it'll end your sensor session

Continued on reverse

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

For peer review only



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.