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# A feasibility randomized control trial for continuous glucose monitoring in type 1 diabetes patients at first-level hospitals in rural Malawi



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# A feasibility randomized control trial for continuous glucose monitoring in type 1 diabetes patients at first-level hospitals in rural Malawi

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**ABSTRACT**

**Introduction:** The majority of people living with type 1 diabetes (PLWT1D) struggle to access high quality care in low-income countries (LICs), and lack access to technologies, including continuous glucose monitoring (CGM), that are considered standard of care in high resource settings. To our knowledge, there are no studies in the literature describing the feasibility or effectiveness of CGM at rural first-level hospitals in LICs.

**Methods and analysis:** This is a three-month, 2:1 open-randomized trial to assess the feasibility and clinical outcomes of introducing CGM to the entire population of 50 PLWT1D in two hospitals in rural Neno, Malawi. Participants in both arms will receive two days of training on diabetes management. One day of training will be the same for both arms, and one will be specific to the diabetes technology. Participants in the intervention arm will receive Dexcom G6 CGM devices with sensors and solar chargers, and patients in the control arm will receive Safe-Accu home glucose meters and logbooks. All patients will have their HbA1c measured and take WHO Quality of Life assessments at study baseline and endline. We will conduct qualitative interviews with a selection of participants from both arms at the beginning and end of study and will interview providers at the end of the study. Our primary outcomes of interest are fidelity to protocols, appropriateness of technology, HbA1c, and severe adverse events.

**Ethics and dissemination:** This study is approved by National Health Sciences Research Committee (NHSRC) of Malawi (IRB Number IR800003905) and the Mass General Brigham (IRB number 2019P003554). Findings will be disseminated to PLWT1D through health education sessions. We will disseminate any relevant findings to clinicians and leadership within our study catchment area and networks. We will publish our findings in an open-access peer-reviewed journal.

Trial Registration number: PACTR202102832069874.

Keywords: Type 1 Diabetes, Continuous Glucose Monitoring, Malawi, Low-Income Country, RCT

**Strengths and limitations of this study:**

- First RCT to study use of CGM in a rural first level hospital in a low-income country
- Will enroll entire population of known people living with type 1 diabetes in two hospitals in Neno District, Malawi
- Will include interviews with patients living with type 1 diabetes and providers to contextualize acceptability and challenges of using CGM
- Because this is the entire population of people living with type 1 diabetes, it is limited sample size

## INTRODUCTION

Type 1 diabetes (T1D) is a severe autoimmune condition where the pancreas produces insufficient insulin.[1] In Sub-Saharan Africa T1D prevalence, while low, is thought to be increasing.[2] People living with type 1 diabetes (PLWT1D) require uninterrupted access to insulin to survive, as well as tools for glucose monitoring and continuous access to education and health care services to attain glycemic control and prevent long term complications. PLWT1D without access to proper care generally do not survive one year.[3] Both premature death and diabetes-related complication rates are significantly higher in low and lower middle income countries due to challenges with access to care and supplies.[4] Ogle and colleagues defined guidelines for minimal, intermediate, and comprehensive levels of care for PLWT1D, and proposed intermediate level of care as an achievable goal for resource-limited settings that could decrease premature mortality and complication rates.[5] Intermediate care includes multiple daily injections of insulin, checking blood glucose 2-4 times per day, consistent point-of-care hemoglobin A1c (HbA1c), complication screening, and a team approach to diabetes education and support.

The majority of PLWT1D are unable to access intermediate care in low-income countries, with care mostly restricted to national or regional centers. [2,4,6-7] Recent efforts have begun to increase access and lower the costs of care by decentralizing services to primary hospitals through nurse-led integrated delivery models called PEN-Plus.[8] Consistent with intermediate care described in Ogle et al., the standard of care within PEN-Plus currently includes self-monitoring of blood glucose (SMBG) by glucose meters. However, we acknowledge that there are challenges in patient adherence to bringing the device and log book to clinic visits. Patients may also not adhere to the SMBG schedule. Thus, there is a need for more innovation at rural decentralized clinics to advance the standard of care particularly around glucose monitoring at home. At this stage, it is critical to establish viable strategies to improve glycemic control for patients with T1D as PEN-Plus is adapted and scaled throughout Africa.

New advancements in blood glucose management technology, namely real-time continuous glucose monitoring (CGM), allow for patients' glucose levels to be automatically recorded throughout the day and reviewed by the patient in real time and at home to look at patterns throughout the day or uploaded for the clinician to review at the clinic. This technology has been shown to significantly reduce HbA1c values and median duration of hypoglycemia by allowing uniform tracking of the glucose concentrations in the body's interstitial fluid.[9] This near real-time glucose data can be used to inform and direct precise diabetes management.[10] A Cochrane review of CGM systems for the management of PLWT1D showed a statistically significant average decline in HbA1c levels six months after baseline for patients who started on CGM therapy at the time of the study.[11] Additionally, a recent international consensus statement on the use of CGM technology in the clinical management of diabetes concluded that continuous glucose monitoring data should be considered for use to help patients with diabetes improve glycemic control provided that appropriate educational and technical support is available.[10] While these studies indicate significant benefits that CGM therapy can achieve in the management of patients with T1D, they are conducted in high-income countries where robust health systems and a higher familiarity with technology and data-informed self-management are more common. Additionally, many of the studies included patients utilizing CGM sensor augmented insulin pump therapy, a therapy not largely available in low-resource settings at this time.

Currently, no data exist on the feasibility and clinical impact of CGM for PLWT1D in rural, low-resource settings, especially in areas that experience a lack of electricity, literacy and data-informed self-management. In one randomized controlled trial (RCT) on the clinical benefits of CGM technology in the management of women with gestational diabetes at an urban tertiary facility in Malaysia, 22 of the 81

eligible participants refused to participate in the study due to inconvenience (n=6) and refusal of the CGM intervention (n=16).[12] Even at this urban facility in a middle-income country, there are potential barriers to the feasibility of delivering CGM technology. An observational study of flash CGM use in PLWT1D in urban East African youth was able to complete follow up on 68 of 78 participants and found CGM to be feasible in this setting [13]. This study aims to assess the feasibility and clinical impact of CGM use among patients with T1D with limited literacy receiving care at rural first-level hospitals in a low-income country.

**Objectives**

The objectives of this study are to: 1) assess the feasibility of CGM use among a rural population of patients with T1D and limited literacy in a low-income country; 2) determine the effectiveness of CGM on diabetes clinical outcomes among patients with T1D in LICs using clinical endpoints; and 3) determine variability in the standard deviation of HbA1C in order to inform further studies.

**METHODS AND ANALYSIS**

This protocol is reported following the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT). This study is registered at Pan African Clinical Trial Registry (www.pactr.org) id: PACTR202102832069874.

**Study Setting**

This study will be conducted at two rural first-level hospitals in Neno, Malawi. Neno District in southern Malawi has a population of about 138,000 people, who mostly rely on subsistence agriculture. Neno has two Ministry of Health (MOH) hospitals: one district hospital in the center of Neno, and a community hospital in Lisungwi. Since 2007, Partners In Health (PIH), a United States-based non-government organization known locally as Abwenzi Pa Za Umoyo (APZU), has partnered with the MOH to improve health care and socioeconomic development in Neno District. In 2018, Neno District opened two advanced non-communicable disease (NCD) clinics at each of the first-level hospitals. The clinics provide high-quality care for complex NCDs, consistent with the PEN-Plus model [8]. Patients with type 1 diabetes are enrolled in this clinic and receive care from mid-level providers (clinical officers) with specialized training in NCDs. In addition, every household in Neno is assigned a Community Health Worker (CHW) who visit households monthly for education and screening for multiple common conditions, enrollment into maternal and chronic care, and accompaniment to clinic. PLWT1D are supported through more frequent visits, when CHWs conduct treatment and adherence counseling, identification of side effects or danger signs, and missed visit tracking.

**Study design**

This is a three-month feasibility 2:1 parallel arm open-randomized control study to assess the feasibility and impact of CGM among PLWT1D in two rural hospitals in Neno, Malawi.

Prior to the start of data collection, NCD clinicians will partake in a one-week training on the study protocol as it applies to the use of CGM, glucose meters, and logbooks. Providers will have the opportunity to wear a Dexcom device as part of their training to familiarize themselves with the technology. Initial education will be followed up by real-time, ongoing digital training every two weeks.

The trial will consist of two arms in a 2:1 ratio (intervention to comparison). In the intervention group participants will be given the CGM Dexcom G6 model with transmitters, receivers, and solar charges.

The comparator group is to be given Safe-Accu glucose meters, Safe-Accu test strips, lancets and locally made logbooks, which are increasingly being used in low-resource settings and are the current standard of care in Neno. This comparator intervention was used as it has been shown to be feasible and effective in LICs [14] and does not require the level of resources or training that CGM does.

At the beginning of the trial, both arms will attend a two-day training for participants, their families, and CHWs. Training related to diabetes management will be adapted from the International Society for Pediatric and Adolescent Diabetes and Life for a Child curriculum.[15] On the first training day, all participants will receive training in a culturally appropriate manner on diabetes management including: diabetes symptom recognition, insulin treatment, managing hypoglycemia, sick day management, blood glucose monitoring, nutritional management, physical activity management, and dispelling of myths and false beliefs surrounding diabetes. On the second day, each arm will receive specialized training related to either CGM or home glucose meters, including a refresher of the first day's material regarding safe diabetes management in the context of using a CGM or glucose meter.

Participants in both groups will be expected to attend at least monthly follow-up clinic visits. For participants in the treatment group, clinicians will use the Dexcom computer software CLARITY to upload CGM data, create reports, and review data to inform their management of T1D.

For those in the control group, participants will be required to bring their glucose meter machines and logbooks to monthly visits, consistent with current practice. During these visits the study staff will assess the utilization of the log book by checking completeness as per the expected number of recordings. The utilization of the glucose meter will be assessed by reviewing the historical memory. To check the validity of the log book records, the records in the log book will be compared by study staff to those in the glucose meter memory including the time and readings of the glucose levels.

All participants will receive routine T1D care including regular blood tests for HbA1c every three months. Thus, all participants will receive HbA1c testing at enrollment and upon conclusion of the study period.

At the beginning and end of the study, we will conduct semi-structured interviews with 3-4 purposively selected participants from both arms to ask about their experiences with living with and managing their T1D and their experience utilizing CGM if in the treatment group.

**Randomization and Allocation**

Sequence generation: Subjects will be individually randomized using a random number table.
Allocation concealment: Allocation will be concealed through the use of sealed envelopes. One person will be responsible for the allocation at all sites, and this person will not have access to the subject records.

**Eligibility Criteria**

We will enroll all eligible participants in the respective T1D programs from the PIH supported districts. Any patient diagnosed with T1D will be eligible to participate. The inclusion and exclusion criteria will be as follows:

- Inclusion criteria: a T1D diagnosis; enrolled in the NCD program at the mentioned PIH-supported MOH facilities
- Exclusion criteria: pregnant; inability of subject or care-provider to use transmitter and applicator

Eligible participants will be identified through electronic medical records, chart review or referred to the study staff by the NCD clinicians. The study staff will then contact the participants either during routine follow up visits or phone calls to obtain informed consent to participate in the study. All participants will be required to sign an informed consent form on the day of enrollment.

**Sample size**

All 50 PLWT1D identified at the two hospitals in Neno will be offered to take part. Figure 1 shows the expected power for examining difference in reduction of HbA1c between arms. Given an expected standard deviation of 1.6 or less we would have 80% power to identify a 1.2% difference in reduction between the treatment arm and the control arm.

**Data collection**

The study is expected to begin recruitment in September 2021. We expect data collection to be completed by January 2022. A T1D research and clinical fellow, who is experienced in CGM care delivery, training, and evaluation, will be on site for the training at the initiation of the study. All participants will complete the intake form on enrollment to include information on duration since diagnosis with T1D, marital status and education level. At baseline and endline all participants will complete the WHO Quality of Life questionnaire and a point-of-care test for HbA1c. We will also conduct chart reviews to obtain information about insulin dosage and dose adjustments.

**Outcomes**

Primary outcomes

*Implementation outcomes*

Fidelity: Variables that reflect the participants' adherence to the per protocol utilization of technology including

a) Percent of time worn
b) Percent of expected blood glucose readings logged
c) Percent of participants who brought log book to clinic during study period
d) Percent of expected times blood sugar test was performed (based on logbooks, home glucose meters, numbers of strips)
e) Percent of expected times CGM and self-monitoring blood glucose (SMBG) information was used to inform lifestyle adjusted interventions.
f) Number of sensors worn

Appropriateness: Factors will be assessed from quantitative and qualitative data. The frequency of technology or battery issues will be measured. Additionally, participants will take part in qualitative interviews at baseline and endline discussing the ease of use and benefits and challenges of CGM technology in their setting.

*Clinical outcomes*

Change in HbA1C: HbA1c in rural Malawi is generally tested via a point-of-care device and requires a lancet-induced drop of capillary blood from the participant's fingertip. The resulting percent value reflects the blood glucose level over the past 1-3 months. This will be measured at study enrollment and upon conclusion of the study period. While percent time in range is considered the gold standard in CGM trials, because in this trial we are unsure what proportion of individuals will be able to successfully use their CGM, we are choosing HbA1c as a primary outcome, as we will be able to measure it in all study participants.
Severe adverse events: Potential adverse events include infection, local skin reaction, bleeding, hospitalization, hypo- and hyperglycemia. Data sources will include readings/reports from CGM and home glucose meters, clinician's reports, and self-reports through logbooks and qualitative interviews.

Secondary outcomes

Acceptability: In qualitative interviews at baseline and endline, participants and clinical providers will discuss their satisfaction with content, complexity, comfort, and delivery of CGM or SMBG technologies.
% Time in range: This value represents the proportion of blood glucose readings observed by the subject which are within the normal range (70-180 mg/dL). This will be measured using uploaded CGM data in the intervention arm.
Average standard deviation in HbA1c: This statistic will determine variability in the standard deviation of HbA1C in order to inform further studies.
Quality of life: WHO Quality of Life surveys will be conducted at the start and conclusion of the study period.

**Statistical methods**

The analysis will be conducted as an intention to treat. We will also conduct a secondary sensitivity per-protocol analysis. For continuous outcomes including HbA1c, we will use ANCOVA models adjusting for baseline levels and site. For binary outcomes we will conduct logistic regressions adjusting for possible confounders including site. For qualitative outcomes we will conduct a narrative synthesis using a thematic analysis.

**Harms**

All participants will be provided an educational session about the project and training on proper disposal of Dexcom sensors and insertion devices. While rates of infection, skin reaction, and traumatic bleeding are extremely low, clinical staff will be available by phone and in-person at health facilities for monitoring and appropriate clinical management. Clear protocols warranting medical attention will be provided to participants. Research staff and clinical teams will be well-versed in proper protocols and/or clinical management for any adverse events. Any reported adverse events will be immediately assessed and documented. A monthly report describing all adverse events will be reviewed by research staff, including the Principal Investigator, and reported to the NCD Unit within the Clinical Services Directorate at the Malawi Ministry of Health.

**Patients and public research involvement**

PLWT1D will be engaged throughout the entire study. As the primary outcome of this research is feasibility and acceptability, perspectives, experiences and views of the technology by PLWT1D is core to the entire study. One of the study co-authors (GF) is living with T1D, and will be involved throughout the design of the protocol, tools, and implementation of the study.

## ETHICS AND DISSEMINATION

The protocol is approved by National Health Sciences Research Committee (NHSRC) of Malawi (IRB Number IR800003905) and the Mass General Brigham (IRB number 2019P003554). All participants will be required to provide signed or fingerprinted informed consent prior to enrolment in the study. Findings will be disseminated to PLWT1D through health education sessions. We will disseminate any relevant findings to clinicians and leadership within our study catchment area and networks. We will publish our findings in an open-access peer-reviewed journal

## AUTHORS' CONTRIBUTIONS

Study and tool design: AJA, TR, FV, CT, GF, AM, EBW, CK, GB, PHP
Manuscript drafting AJA, LD, PHP, GB
All authors contributed to the final manuscript

## COMPETING INTEREST STATEMENT

There are no competing interests declared by the study investigators.

## FUNDING STATEMENT

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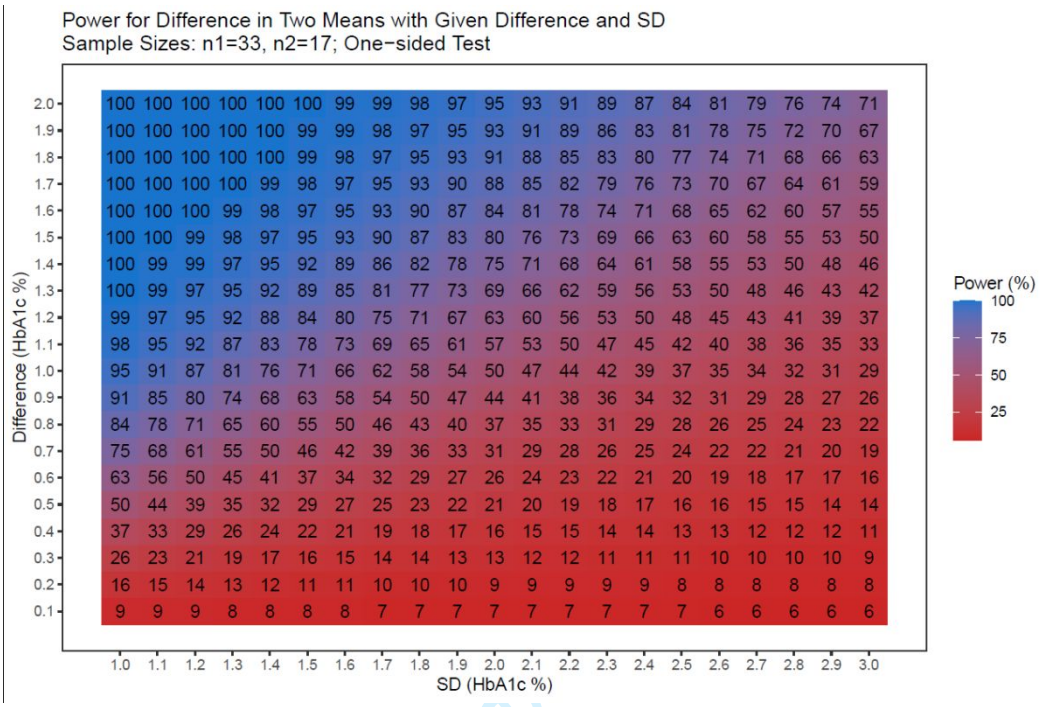


Figure 1. Power table showing expected power for range of changes in HbA1c levels for different standard deviations.

# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | 1 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 2 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 3-4 |
| | 2b | Specific objectives or hypotheses | 4 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 4-5 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | n/a |
| Participants | 4a | Eligibility criteria for participants | 5-6 |
| | 4b | Settings and locations where the data will be collected | 4 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 4-6 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 6-7 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | n/a |
| Sample size | 7a | How sample size was determined | 6 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | n/a |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 5 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 5 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 5 |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | n/a |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those | n/a |

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| | | assessing outcomes) and how | |
| | 11b | If relevant, description of the similarity of interventions | n/a |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 7 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | n/a |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | n/a |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | n/a |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | n/a |
| | 14b | Why the trial ended or was stopped | n/a |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | n/a |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | n/a |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | n/a |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | n/a |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | n/a |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | n/a |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | n/a |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | n/a |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | n/a |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | 4 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | n/a |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | 8 |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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## ABSTRACT

**Introduction:** The majority of people living with type 1 diabetes (PLWT1D) struggle to access high quality care in low-income countries (LICs), and lack access to technologies, including continuous glucose monitoring (CGM), that are considered standard of care in high resource settings. To our knowledge, there are no studies in the literature describing the feasibility or effectiveness of CGM at rural first-level hospitals in LICs.

**Methods and analysis:** This is a three-month, 2:1 open-randomized trial to assess the feasibility and clinical outcomes of introducing CGM to the entire population of 50 PLWT1D in two hospitals in rural Neno, Malawi. Participants in both arms will receive two days of training on diabetes management. One day of training will be the same for both arms, and one will be specific to the diabetes technology. Participants in the intervention arm will receive Dexcom G6 CGM devices with sensors and solar chargers, and patients in the control arm will receive Safe-Accu home glucose meters and logbooks. All patients will have their HbA1c measured and take WHO Quality of Life assessments at study baseline and endline. We will conduct qualitative interviews with a selection of participants from both arms at the beginning and end of study and will interview providers at the end of the study. Our primary outcomes of interest are fidelity to protocols, appropriateness of technology, HbA1c, and severe adverse events.

**Ethics and dissemination:** This study is approved by National Health Sciences Research Committee (NHSRC) of Malawi (IRB Number IR800003905) and the Mass General Brigham (IRB number 2019P003554). Findings will be disseminated to PLWT1D through health education sessions. We will disseminate any relevant findings to clinicians and leadership within our study catchment area and networks. We will publish our findings in an open-access peer-reviewed journal.

Trial Registration number: PACTR202102832069874.

Version 1.1 Date 27 November, 2021


Keywords: Type 1 Diabetes, Continuous Glucose Monitoring, Malawi, Low-Income Country, RCT

**Strengths and limitations of this study:**

- First RCT to study use of CGM in a rural first level hospital in a low-income country
- Will enroll entire population of known people living with type 1 diabetes in two hospitals in Neno District, Malawi
- Will include interviews with patients living with type 1 diabetes and providers to contextualize acceptability and challenges of using CGM
- Because this is the entire population of people living with type 1 diabetes, it is limited sample size

## INTRODUCTION

Type 1 diabetes (T1D) is a severe autoimmune condition where the pancreas produces insufficient insulin.[1] In Sub-Saharan Africa T1D prevalence, while low, is thought to be increasing.[2] People living with type 1 diabetes (PLWT1D) require uninterrupted access to insulin to survive, as well as tools for glucose monitoring and continuous access to education and health care services to attain glycemic control and prevent long term complications. PLWT1D without access to proper care generally do not survive one year.[3] Both premature death and diabetes-related complication rates are significantly higher in low and lower middle income countries due to challenges with access to care and supplies.[4] Ogle and colleagues defined guidelines for minimal, intermediate, and comprehensive levels of care for PLWT1D, and proposed intermediate level of care as an achievable goal for resource-limited settings that could decrease premature mortality and complication rates.[5] Intermediate care includes multiple daily injections of insulin, checking blood glucose 2-4 times per day, consistent point-of-care hemoglobin A1c (HbA1c), complication screening, and a team approach to diabetes education and support.

The majority of PLWT1D are unable to access intermediate care in low-income countries, with care mostly restricted to national or regional centers. [2,4,6-7] Recent efforts have begun to increase access and lower the costs of care by decentralizing services to primary hospitals through nurse-led integrated delivery models called PEN-Plus.[8] Consistent with intermediate care described in Ogle et al., the standard of care within PEN-Plus currently includes self-monitoring of blood glucose (SMBG) by glucose meters. However, we acknowledge that there are challenges in patient adherence to bringing the device and log book to clinic visits. Patients may also not adhere to the SMBG schedule. Thus, there is a need for more innovation at rural decentralized clinics to advance the standard of care particularly around glucose monitoring at home. At this stage, it is critical to establish viable strategies to improve glycemic control for patients with T1D as PEN-Plus is adapted and scaled throughout Africa.

New advancements in blood glucose management technology, namely real-time continuous glucose monitoring (CGM), allow for patients' glucose levels to be automatically recorded throughout the day and reviewed by the patient in real time and at home to look at patterns throughout the day or uploaded for the clinician to review at the clinic. This technology has been shown to significantly reduce HbA1c values and median duration of hypoglycemia by allowing uniform tracking of the glucose concentrations in the body's interstitial fluid.[9] This near real-time glucose data can be used to inform and direct precise diabetes management.[10] A Cochrane review of CGM systems for the management of PLWT1D showed a statistically significant average decline in HbA1c levels six months after baseline for patients who started on CGM therapy at the time of the study.[11] Additionally, a recent international consensus statement on the use of CGM technology in the clinical management of diabetes concluded that continuous glucose monitoring data should be considered for use to help patients with diabetes improve glycemic control provided that appropriate educational and technical support is available.[10] While these studies indicate significant benefits that CGM therapy can achieve in the management of patients with T1D, they are conducted in high-income countries where robust health systems and a higher familiarity with technology and data-informed self-management are more common. Additionally, many of the studies included patients utilizing CGM sensor augmented insulin pump therapy, a therapy not largely available in low-resource settings at this time.

Currently, no data exist on the feasibility and clinical impact of CGM for PLWT1D in rural, low-resource settings, especially in areas that experience a lack of electricity, literacy and data-informed self-management. In one randomized controlled trial (RCT) on the clinical benefits of CGM technology in the management of women with gestational diabetes at an urban tertiary facility in Malaysia, 22 of the 81

eligible participants refused to participate in the study due to inconvenience (n=6) and refusal of the CGM intervention (n=16).[12] Even at this urban facility in a middle-income country, there are potential barriers to the feasibility of delivering CGM technology. An observational study of flash CGM use in PLWT1D in urban East African youth was able to complete follow up on 68 of 78 participants and found CGM to be feasible in this setting [13]. This study aims to assess the feasibility and clinical impact of CGM use among patients with T1D with limited literacy receiving care at rural first-level hospitals in a low-income country.

**Objectives**

The objectives of this study are to: 1) assess the feasibility of CGM use among a rural population of patients with T1D and limited literacy in a low-income country; 2) determine the effectiveness of CGM on diabetes clinical outcomes among patients with T1D in LICs using clinical endpoints; and 3) determine variability in the standard deviation of HbA1C in order to inform further studies.

**METHODS AND ANALYSIS**

This protocol is reported following the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT). This study is registered at Pan African Clinical Trial Registry (www.pactr.org) id: PACTR202102832069874.

**Study Setting**

This study will be conducted at two rural first-level hospitals in Neno, Malawi. Neno District in southern Malawi has a population of about 138,000 people, who mostly rely on subsistence agriculture. Neno has two Ministry of Health (MOH) hospitals: one district hospital in the center of Neno, and a community hospital in Lisungwi. Since 2007, Partners In Health (PIH), a United States-based non-government organization known locally as Abwenzi Pa Za Umoyo (APZU), has partnered with the MOH to improve health care and socioeconomic development in Neno District. In 2018, Neno District opened two advanced non-communicable disease (NCD) clinics at each of the first-level hospitals. The clinics provide high-quality care for complex NCDs, consistent with the PEN-Plus model [8]. Patients with type 1 diabetes are enrolled in this clinic and receive care from mid-level providers (clinical officers) with specialized training in NCDs. All insulin is provided free of charge to all patients at their routine monthly appointments. In addition, every household in Neno is assigned a Community Health Worker (CHW) who visit households monthly for education and screening for multiple common conditions, enrollment into maternal and chronic care, and accompaniment to clinic. PLWT1D are supported through more frequent visits, when CHWs conduct treatment and adherence counseling, identification of side effects or danger signs, and missed visit tracking.

**Study design**

This is a three-month feasibility 2:1 parallel arm open-randomized control study to assess the feasibility and impact of CGM among PLWT1D in two rural hospitals in Neno, Malawi.

Prior to the start of data collection, NCD clinicians will partake in a one-week training on the study protocol as it applies to the use of CGM, glucose meters, and logbooks. Providers will have the opportunity to wear a Dexcom device as part of their training to familiarize themselves with the technology. Initial education will be followed up by real-time, ongoing digital training every two weeks.

The trial will consist of two arms in a 2:1 ratio (intervention to comparison). In the intervention group participants will be given the CGM Dexcom G6 model with transmitters, receivers, and solar charges.

The comparator group is to be given Safe-Accu glucose meters, Safe-Accu test strips, lancets and locally made logbooks, which are increasingly being used in low-resource settings and are the current standard of care in Neno. This comparator intervention was used as it has been shown to be feasible and effective in LICs [14] and does not require the level of resources or training that CGM does.

At the beginning of the trial, both arms will attend a two-day training for participants, their families, and CHWs. Training related to diabetes management will be adapted from the International Society for Pediatric and Adolescent Diabetes and Life for a Child curriculum.[15] On the first training day, all participants will receive training in a culturally appropriate manner on diabetes management including: diabetes symptom recognition, insulin treatment, managing hypoglycemia, sick day management, blood glucose monitoring, nutritional management, physical activity management, and dispelling of myths and false beliefs surrounding diabetes. On the second day, each arm will receive specialized training related to either CGM or home glucose meters, including a refresher of the first day's material regarding safe diabetes management in the context of using a CGM or glucose meter.

Participants in both groups will be expected to attend at least monthly follow-up clinic visits. For participants in the treatment group, clinicians will use the Dexcom computer software CLARITY to upload CGM data, create reports, and review data to inform their management of T1D.

For those in the control group, participants will be required to bring their glucose meter machines and logbooks to monthly visits, consistent with current practice. During these visits the study staff will assess the utilization of the log book by checking completeness as per the expected number of recordings. The utilization of the glucose meter will be assessed by reviewing the historical memory. To check the validity of the log book records, the records in the log book will be compared by study staff to those in the glucose meter memory including the time and readings of the glucose levels.

In line with current practice, we will not be encouraging patients to self-titrate. We are instead focusing on encouraging providers to help patients problem-solve possible scenarios around diabetes management that may require adjusting insulin doses (e.g., food insecurity and illness). All participants will receive routine T1D care including regular blood tests for HbA1c every three months. Thus, all participants will receive HbA1c testing at enrollment and upon conclusion of the study period.

At the beginning and end of the study, we will conduct semi-structured interviews with 3-4 purposively selected participants from both arms to ask about their experiences with living with and managing their T1D and their experience utilizing CGM if in the treatment group.

**Randomization and Allocation**

Sequence generation: The research coordinator based in Neno will randomize subjects using a random number table.
Allocation concealment: Allocation will be concealed through the use of sealed envelopes. The research coordinator will be responsible for the allocation at all sites, and this person will not have access to the subject records.
Due to the nature of the study blinding will not be possible.

**Eligibility Criteria**

We will enroll all eligible participants in the respective T1D programs from the PIH supported districts. Any patient diagnosed with T1D will be eligible to participate. The inclusion and exclusion criteria will be as follows:

- Inclusion criteria: a T1D diagnosis; enrolled in the NCD program at the mentioned PIH-supported MOH facilities
- Exclusion criteria: pregnant; inability of subject or care-provider to use transmitter and applicator

Eligible participants will be identified through electronic medical records, chart review or referred to the study staff by the NCD clinicians. The study staff will then contact the participants either during routine follow up visits or phone calls to obtain informed consent to participate in the study. All participants will be required to sign an informed consent form on the day of enrollment (Appendix A). Assent will be collected from children under the age of 18 (Appendix B). Patients will be enrolled regardless of literacy. No patients with mental impairment will be included.

**Sample size**

All 50 PLWT1D identified at the two hospitals in Neno will be offered to take part. Figure 1 shows the expected power for examining difference in reduction of HbA1c between arms. Given an expected standard deviation of 1.6 or less we would have 80% power to identify a 1.2% difference in reduction between the treatment arm and the control arm.

**Data collection**

The study is expected to begin recruitment in March 2022. We expect data collection to be completed by June 2022. A T1D research and clinical fellow, who is experienced in CGM care delivery, training, and evaluation, will be on site for the training at the initiation of the study. All participants will complete the intake form on enrollment to include information on duration since diagnosis with T1D, marital status and education level. At baseline and endline all participants will complete the WHO Quality of Life questionnaire and a point-of-care test for HbA1c. We will also conduct chart reviews to obtain information about insulin dosage and dose adjustments.

**Outcomes**

Primary outcomes

*Implementation outcomes*

Fidelity: Variables that reflect the participants' adherence to the per protocol utilization of technology including

a) Percent of time worn
b) Percent of expected blood glucose readings logged
c) Percent of participants who brought log book to clinic during study period
d) Percent of expected times blood sugar test was performed (based on logbooks, home glucose meters, numbers of strips)
e) Percent of expected times CGM and self-monitoring blood glucose (SMBG) information was used to inform lifestyle adjusted interventions.

f) Number of sensors worn

Appropriateness: Factors will be assessed from quantitative and qualitative data. The frequency of technology or battery issues will be measured. Additionally, participants will take part in qualitative interviews at baseline and endline discussing the ease of use and benefits and challenges of CGM technology in their setting.

*Clinical outcomes*

Change in HbA1C: HbA1c in rural Malawi is generally tested via a point-of-care device and requires a lancet-induced drop of capillary blood from the participant's fingertip. The resulting percent value reflects the blood glucose level over the past 1-3 months. This will be measured at study enrollment and upon conclusion of the study period. While percent time in range is considered the gold standard in CGM trials, because in this trial we are unsure what proportion of individuals will be able to successfully use their CGM, we are choosing HbA1c as a primary outcome, as we will be able to measure it in all study participants.

Severe adverse events: Potential adverse events include infection, local skin reaction, bleeding, hospitalization, hypo- and hyperglycemia. Data sources will include readings/reports from CGM and home glucose meters, clinician's reports, and self-reports through logbooks and qualitative interviews.

Secondary outcomes

Acceptability: In qualitative interviews at baseline and endline, participants and clinical providers will discuss their satisfaction with content, complexity, comfort, and delivery of CGM or SMBG technologies.

% Time in range: This value represents the proportion of blood glucose readings observed by the subject which are within the normal range (70-180 mg/dL). This will be measured using uploaded CGM data in the intervention arm.

Average standard deviation in HbA1c: This statistic will determine variability in the standard deviation of HbA1C in order to inform further studies.

Quality of life: WHO Quality of Life surveys will be conducted at the start and conclusion of the study period.

**Statistical methods**

The analysis will be conducted as an intention to treat. We will also conduct a secondary sensitivity per-protocol analysis. For continuous outcomes including HbA1c, we will use ANCOVA models adjusting for baseline levels and site. For binary outcomes we will conduct logistic regressions adjusting for possible confounders including site. For qualitative outcomes we will conduct a narrative synthesis using a thematic analysis.

**Harms**

All participants will be provided an educational session about the project and training on proper disposal of Dexcom sensors and insertion devices. While rates of infection, skin reaction, and traumatic bleeding are extremely low, clinical staff will be available by phone and in-person at health facilities for monitoring and appropriate clinical management. Clear protocols warranting medical attention will be provided to participants. Research staff and clinical teams will be well-versed in proper protocols and/or clinical

management for any adverse events. Any reported adverse events will be immediately assessed and documented. A monthly report describing all adverse events will be reviewed by research staff, including the Principal Investigator, and reported to the NCD Unit within the Clinical Services Directorate at the Malawi Ministry of Health.

All data will be stored in password protected files and/or computers in locked research offices and the patient's CGM receiver. All patients will be trained to keep receivers with them at all times and not share the device with others. Any transfer of data between sites will occur via password protected and encrypted e-mail accounts housed within the participating institutions

**Patients and public research involvement**

PLWT1D will be engaged throughout the entire study. As the primary outcome of this research is feasibility and acceptability, perspectives, experiences and views of the technology by PLWT1D is core to the entire study. One of the study co-authors (GF) is living with T1D, and will be involved throughout the design of the protocol, tools, and implementation of the study.

**ETHICS AND DISSEMINATION**

The protocol is approved by National Health Sciences Research Committee (NHSRC) of Malawi (IRB Number IR800003905) and the Mass General Brigham (IRB number 2019P003554). All participants will be required to provide signed or fingerprinted informed consent to NCD clinic staff prior to enrolment in the study. Findings will be disseminated to PLWT1D through health education sessions. We will disseminate any relevant findings to clinicians and leadership within our study catchment area and networks. We will publish our findings in an open-access peer-reviewed journal. Any deviations from the study protocol will be communicated to investigators and participants, as well as clearly outlined in any publications.

**AUTHORS' CONTRIBUTIONS**

Study and tool design: AJA, TR, FV, CT, GF, AM, EBW, CK, GB, PHP
Manuscript drafting AJA, LD, PHP, GB
All authors contributed to the final manuscript

**COMPETING INTEREST STATEMENT**

There are no competing interests declared by the study investigators.

**FUNDING STATEMENT**

This work was supported by the Leona M. and Harry B. Helmsley Charitable Trust grant number 2105-04638. Dexcom provided CGM Dexcom 6 glucose meters and sensors for the project free of charge. The funders had no input into the design or conduct of the study

Figure legend:
Figure 1. Power table showing expected power for range of changes in HbA1c levels for different standard deviations

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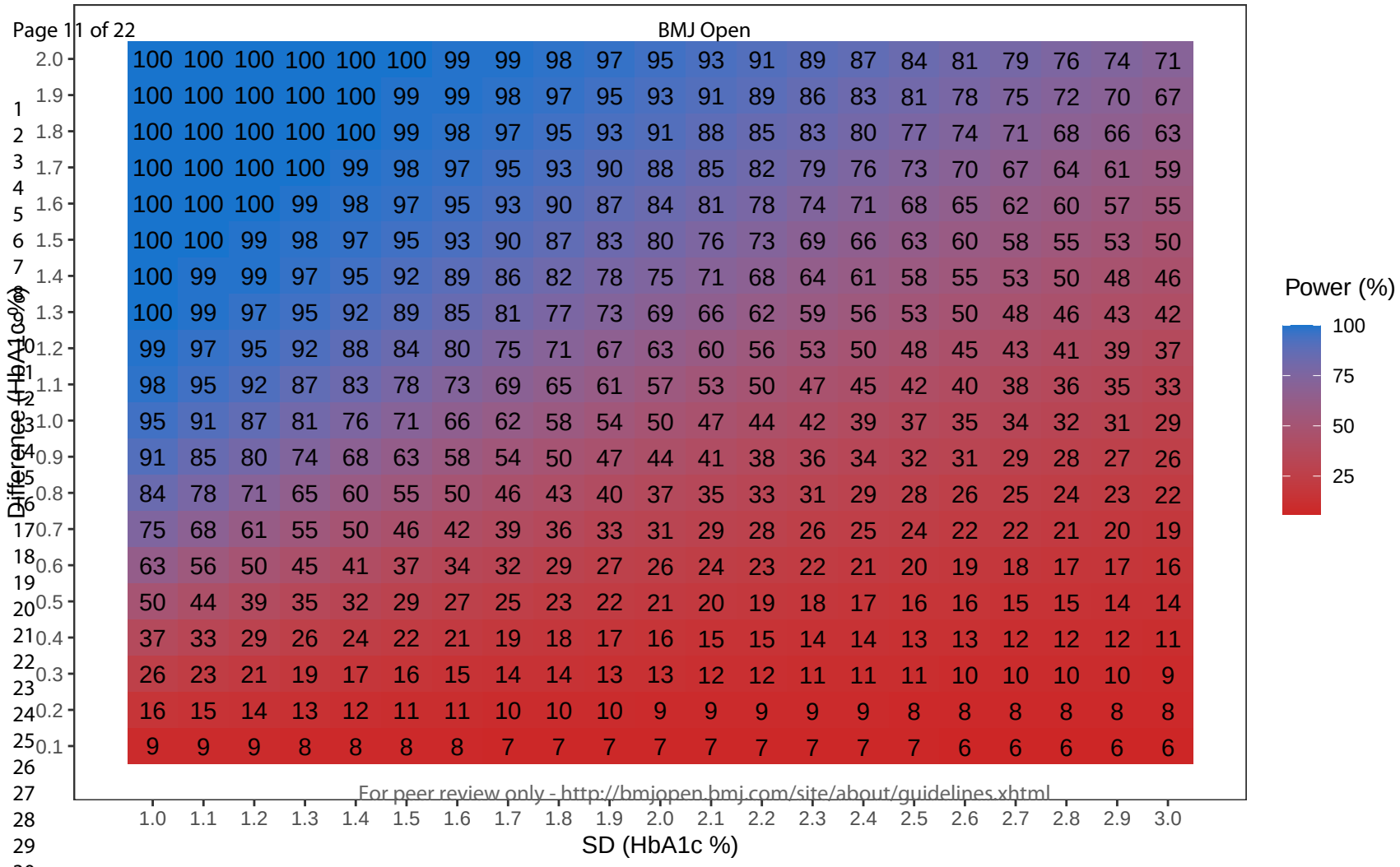


# MINISTRY OF HEALTH
# NATIONAL HEALTH SCIENCES RESEARCH COMMITTEE



## IMPORTANT ELEMENTS IN AN INFORMED CONSENT FORM

**Study title:** A feasibility CGM trial for patients with type 1 diabetes followed at a rural, first-level hospital in a low-income country

**Name and Contacts of Principal Investigator:**

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**NHSRC Contacts**

NHSRC contact details should be indicated immediately after details of the PI

**Introduction**

Treatment for Type 1 diabetes (T1D) is currently reaching very few of those affected in low-income countries. Mostly care is restricted to national or regional centers. Recent efforts have begun to increase access and lower the costs of care by decentralizing services to primary hospitals through nurse-led integrated delivery models (Package of Essential Noncommunicable Disease Interventions/PEN-Plus). These care delivery models are in the process of being codified in collaboration with the World Health Organization. At this stage, it is critical to establish viable strategies to improve glycemic control for patients with T1D as PEN-Plus is adapted and scaled throughout Africa.

New advancements in blood glucose monitoring and management technology, namely real-time continuous glucose monitoring (rtCGM), allow for patients' glucose levels to be automatically measured and recorded throughout the day and then reviewed by the patient at home or uploaded for the clinician to review at the clinic. Additionally, some CGM systems have built in alarms that are set to alert patients if their glucose levels fall below or rise above a certain number, and some even predict hypoglycemic episodes minutes before they even happen. This technology has been shown to significantly reduce HbA1c values and median duration of hypoglycemia by allowing uniform tracking of the glucose concentrations in the body's interstitial

fluid and alerting patients when or before they experience hypoglycemia by allowing them to treat low blood sugars. This near real-time glucose data can be used to inform and direct precise diabetes management. Cochrane review of CGM systems for the management of patients with T1D across all age groups showed a statistically significant average decline in HbA1c levels six months after baseline for patients who started on CGM therapy at the time of the study. While this study indicates significant benefits CGM therapy can achieve in the management of patients with T1D, all of the studies included in the review were conducted in high income countries where robust health systems and a higher familiarity with technology and data informed self-management are more common. Additionally, many of the studies included patients utilizing CGM sensor augmented insulin pump therapy, a therapy not largely available in low resource settings at this time.

Currently, no data exist on the feasibility and clinical impact of rtCGM for patients with T1D managing with multiple daily injections in rural, low resource settings especially in areas that experience a lack of electricity, literacy and data informed self-management. In one RCT study on the clinical benefits of CGM technology in the management of women with gestational diabetes at an urban tertiary facility in Malaysia, 22 of the 81 eligible participants refused to participate in the study due to inconvenience (n=6) and refusal of the CGM intervention (n=16) (4). Even at this urban facility in a middle-income country, there are potential barriers to the feasibility of delivering CGM technology. This study aims to assess the feasibility and clinical impact of CGM use among largely illiterate, patients with T1D receiving care at rural first-level hospitals in a low-income country, namely Malawi.

**Purpose**

This proposed research will help us understand the feasibility and clinical effectiveness of continuous glucose monitor (CGM) use among a largely illiterate rural population of patients with T1D, and the feasibility of CGM technology in rural health facilities and homes to explore viable strategies to improve glycemic control for patients with T1D in Malawi. This study is a 3-month, 2:1 parallel arm closed randomized study of any patient with a T1D diagnosis that is enrolled in the NCD program at two district hospitals in Neno District, Malawi.

**Procedure**

Training of NCD clinicians: Prior to the start of data collection, the NCD clinicians at the four country sites will be trained on the study protocol as it applies to the use of CGM and SMBG by subjects and clinicians as well as use of glucose meter and logbooks.

Participants in the study will be randomized into two groups: those who will be using home glucometers to measure their blood sugars and those who will be using CGM technology to measure their blood sugars. Participants will be randomly assigned based on chance to either group while ensuring that two-

thirds of all participants are in the CGM group and one-third of all participants are in the home glucometer group. Both the control and treatment groups will be expected to have monthly follow-up clinic visits. Clinicians will use the CLARITY-based data on the computer as one of the tools for managing type 1 diabetes. Additionally, during the monthly follow-up clinic visit, the clinician and/or study staff will download the last month's data from the Dexcom 6 Receiver to be analyzed via the CLARITY software. If deemed medically necessary, the clinician will recommend any dose adjustments on the day of reviewing the data.

For those in the control group, subjects will be required to carry along their glucose meter machines and logbooks. During these visits the study staff will assess the utilization of the log book by checking completeness as per the expected number of recordings. The utilization of the glucose meter will be assessed by assessing the historical memory. To check the validity of the log book records, the records in the log book will be compared by study staff to those in the glucose meter memory including the time and readings of the glucose levels.

For all study subjects, patients will receive routine T1D care including regular blood tests for HbA1c every 3 months. Thus, all patients will receive HbA1c testing at enrollment and upon conclusion of the study period.

Baseline and endline assessments will be conducted in both arms and will include:

a. Complete the intake form: This will include information on duration since diagnosis with T1D, marital status and education level.

b. Complete the WHO quality of life questionnaire

c. Point of care test for the HbA1c (to be performed by clinical staff)

d. Qualitative interviews will be performed on a sample of subjects to assess their baseline diabetes management prior to study. The interviews will be facilitated by trained study staff.

The following data collection methods are described by outcomes:

- *Clinical outcomes:*

  *HbA1c:* measured at point of care every at baseline and three months.

  *All-cause mortality:* This will be conducted by endline surveys with subjects; if the subject is not available, then the clinical team will be asked to provide last known subject status

  *% Time in range:* Measured using logbooks and CGM reports

*Quality of Life:* WHO QoL survey will be conducted by trained research staff

*Severe adverse events:* These will be measured from logbooks and self-reports

- *Implementation outcomes:*

*Appropriateness and acceptability*: We will conduct semi-structured interviews with 12 purposefully selected participants in each arm (3 from each site) at baseline and endline. In both baseline and endline interviews we will ask questions about their experiences with T1D, self-management, and experiences with adverse events.

In endline interviews we will ask about their experiences with filling out logbooks, and their experiences with the home glucometers and CGM.

*Fidelity*: Fidelity will be measured by logbooks (control arm) and from the CGM and SBGM (intervention arm). We will assess to see:

a) % of expected blood glucose readings logged

b) % of participants who brought log book to clinic during study period

c) % of expected times blood sugar test was performed (based on logbooks, home glucometers, numbers of strips, CGM)

d) % of expected times CGM and SBGM information was used to inform lifestyle adjusted interventions.

**Benefits**

Participants in the study could experience a reduction in HbA1c level, a decrease hypoglycemic events, increased detection of blood glucose trends, better informed treatment decisions and insulin dose adjustments, a better understanding the effects of diet, exercise, stress, illness, etc., on blood glucose, a decrease in the need for finger sticks, increased awareness of hypoglycemia and hyperglycemic events via predictive alarms, increased peace of mind for caregivers and patients, especially at night.

**Risks**

Participants in the study could experience a slight discomfort with application of the sensor, discomfort with the device being on the body, frustration with the sensor falling off, minor skin irritation from the adhesive, missed blood glucose information if the signal is lost or the receiver is not working, inaccurate blood glucose readings compared to venous blood glucose, or feeling overwhelmed from the increased data.

**Privacy and Confidentiality**

Subjects' data will be entered on an electronic database using study specific identification numbers to maintain patient's confidentiality. Computerized data will be accessible only by password and stored in a secure office setting. No subject identifiers will be used in data analysis or dissemination of reports. Data will be reported in aggregate measures that cannot be linked back to any individual participant. Recorded interviews and study records that identify participants will be kept in a secure cabinet that can only be accessed by the study staff.

Each study hospital will have a password-protected laptop with CLARITY application installed. This application will house data that was obtained via sync with the subjects' receiver-based data with physical cable. At the end of the study period, de-identified data will be exported from the laptops (CLARITY application) as a Microsoft Excel file. All computers will be encrypted.

**Study Approval**

Harvard Medical School Institutional Review Board, Boston, MA, USA

National Health Sciences Research Committee, Malawi

**Consent and Signature**

Indicate where the participant, data collector and witness should sign

Participant Signature_____

Data Collector Signature_____

Witness Signature_____

**Study site**

Two District Hospitals in Neno, Malawi

Participant ID: _____

| |
|---|
| Protocol Title: **A feasibility CGM trial for patients with type 1 diabetes followed at a rural, first-level hospital in a low-income country** |
| Principal Investigator: Alma Adler |
| Description of Participant Population: Patients and families of people with type 1 diabetes |
| Version Date: June 25, 2021 |

My name is Todd Ruderman. I am a clinician at Neno District Hospital. I am trying to learn whether your daily life with type 1 diabetes would be improved with Continuous Glucose Monitoring (CGM) or home glucometer technology.

I am asking you and other children to take part in my research study. A research study is a way to learn more about something. You are being asked to join this research study because you have type 1 diabetes.

If you agree to join this study, during your routine medical appointments you will be asked to be interviewed by our staff about your experiences with diabetes, as well as your experiences with doctors and nurses. We expect this to take about an hour, but you can leave at any time. You will also be able to use some helpful new devices that will help you know your blood sugar levels throughout your day. These devices are called continuous glucose monitors, and they have never been used in Malawi or other similar contexts before.

You might feel a little discomfort with using this new technology so you are able to stop participating in the study at any time, and we will have nurses who can help you get back to your usual care. We will do everything that we can to make sure that anything you say will be kept confidential between us. We do think that these new devices could help you manage your diabetes and also help your doctor do their job better by understanding what you need throughout your normal daily life.

You do not have to join this study. It is up to you. You can say okay now and change your mind later. All you have to do is tell us you want to stop. No one will be mad at you if you don't want to be in the study or if you join the study and change your mind later and stop. You may talk to your mom or dad if you want. Before you say **yes or no** to being in this study, we will answer any questions you have. If you join the study, you can ask questions at any time. Just tell the researcher when you see them or contact me, Todd Ruderman, at Neno District Hospital.

If you sign your name below, it means that you agree to take part in this research study.

**Child/Adolescent Assent**

_____ _____
Signature of Study Participant Date

_____ _____
Signature of Researcher Date


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Page # |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2,4 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 4 |
| Protocol version | 3 | Date and version identifier | 2 |
| Funding | 4 | Sources and types of financial, material, and other support | 8 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 8 |
| | 5b | Name and contact information for the trial sponsor | 8 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 8 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | n/a |
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 3-4 |
| | 6b | Explanation for choice of comparators | 5 |
| Objectives | 7 | Specific objectives or hypotheses | 4 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 4-5 |

| | | | |
|---|---|---|---|
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 4 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 5-6 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 4-5 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 7 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 5 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | n/a |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 6-7 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 6 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 6 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 6 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 5 |

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| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 5 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 5 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 5 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | n/a |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 6-7 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 7 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 6-7 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 7 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 7 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 7 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 7-8 |

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|---|---|---|---|
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 7 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | n/a |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 8 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 8 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 8 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 8 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 8 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | n/a |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 8 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 8 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | |

**Appendices**

| | | | |
|---|---|---|---|
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.