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Human versus Analogue Insulin for Youth with Type 1 Diabetes in Low-Resource Settings (HumAn-1): protocol for a randomised controlled trial

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ABSTRACT

Introduction Long-acting insulin analogues are the standard of care for people with type 1 diabetes (T1D) in high-income countries but remain largely inaccessible and understudied in low-resource settings. In settings where glycaemic control is typically poor and food insecurity is common, long-acting insulin analogues may offer tangible clinical benefits for people with T1D. To determine whether insulin glargine, a long-acting insulin analogue, reduces the risk of serious hypoglycaemia and/or improves glycaemic time-in-range (TIR) versus human insulin regimens in this population, we are conducting the Human vs Analogue Insulin for Youth with Type 1 Diabetes in Low-Resource Settings randomised controlled trial.

Methods and analysis This is a 1:1 randomised, parallel-group clinical trial comparing biosimilar insulin glargine with human insulin (Neutral Protamine Hagedorn (NPH) or premixed 70/30 insulin) in 400 youth with type 1 diabetes (T1D) recruiting in Dhaka, Bangladesh (n=250) and Mwanza, Tanzania (n=150). Blinded continuous glucose monitors will be used to assess glycaemic control in both study arms over 14-day periods at baseline and at 3, 6 and 12 months after randomisation. The co-primary outcomes are the per cent time in serious hypoglycaemia (<54 mg/dL) and TIR (70–180 mg/dL) at 6 months of follow-up. Secondary outcomes include TIR at 12 months and time-in-hypoglycaemia, time-above-range, nocturnal hypoglycaemic events and glycaemic control (ie, haemoglobin A1C (HbA1c)) at 6- and 12-months of follow-up. Treatment satisfaction and quality of life are assessed at baseline, 6- and 12 month follow-up. Additionally, the study is conducting qualitative interviews, quantitative assessments of treatment satisfaction and quality of life, as well as assessing the cost-effectiveness of analogue insulin use in low-resource settings.

Ethics and dissemination This study was approved by the Institutional Review Board at the University of Pittsburgh (STUDY21110122), the National Health Research Ethics Committee at the National Institute for Medical Research in Tanzania (NIMR/HQ/R.8a/Vol.IX/4265) and the Ethical Review Committee (ERC) of Diabetic Association of Bangladesh (BADAS-ERC/EC/22/405). Research findings will be shared by the local partner organisations and institutions with relevant stakeholders including youth living with diabetes, policy makers, healthcare workers and the general public. Findings will also be shared at local, regional and international scientific meetings.

Trial registration number ClinicalTrials.gov: NCT05614089.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Human vs Analogue Insulin for Youth with Type 1 Diabetes in Low-Resource Settings study will compare the impact of long-acting insulin analogues to human insulin among youth with type 1 diabetes living in low-resource settings on a variety of outcomes of interest to patients, providers and policy makers, including glycaemic time-in-range, severe hypoglycaemia, haemoglobin A1c (HbA1c), quality of life, healthcare costs and cost-effectiveness.

⇒ The robust methodological design will integrate both quantitative methods (eg, randomised trial design, use of continuous glucose monitors and HbA1c tests) and qualitative methods (eg, in-depth semi-structured interviews with over 120 participants, caregivers, health workers and stakeholders) to enhance the reliability and applicability of the findings to inform global diabetes policy.

⇒ Study sites in South Asia and East Africa provide geographically and culturally diverse perspectives among populations under-represented in research involving youth with T1D.

⇒ Results from participants recruited from larger referral centres where this study is taking place may not be generalisable to other low-resource settings.

INTRODUCTION

In high-income countries, the average additional life expectancy of a 10-year-old diagnosed with type 1 diabetes (T1D) is 60–70 years.[1] In lower-income countries, however, this is reduced to as little as 7 years due to inadequate access to insulin, other supplies

and healthcare workers skilled in T1D care, with many dying at or soon after clinical onset.[1–4]

Long-acting insulin analogues have become part of the standard of care for people with T1D in high-income countries.[5–8] In low-resource or humanitarian settings where glycaemic control is typically suboptimal and food insecurity is common, these insulins may offer significant clinical benefits for people with T1D compared with human insulin, such as reducing nocturnal hypoglycaemic events.[9–13] Glargine, a long-acting insulin analogue with a duration of approximately 24 hours, can be injected once a day and has a smoother time-action profile compared with human basal insulin formulations (eg, NPH and premixed 70/30), which may lead to greater lability of blood glucose levels. Despite these benefits, insulin analogues remain unavailable or unaffordable for much of the global population, with human insulins remaining the mainstay for diabetes care in low-resource settings.[1 14–20]

In 2017 and 2019, applications to add long-acting insulin analogues to the WHO's Model List of Essential Medicines (EML) were rejected due to low-quality evidence of superiority when compared against human insulins and an unfavourable cost-effectiveness profile. After considerable debate, they were eventually added to the EML in 2021, although the decision remains controversial as the WHO concluded that the 'magnitude of clinical benefit of long-acting insulin analogues over human insulin for most clinical outcomes was small.'[21]

Most evidence comparing long-acting insulin analogues to human insulin regimens comes from high-income settings. Existing efforts to overcome the two-tiered system of global diabetes care—where insulin analogues are used in high-income settings and human insulins are used for much of the world's poor—are hampered by a lack of evidence from low-resource settings.[10 22 23] Moreover, while conclusive evidence for the clinical superiority of insulin analogues is lacking, many people with diabetes and global advocates strongly prefer newer analogue insulins.[7 8 13 24–26] This preference is due in part to their added convenience and reduced risk of hypoglycaemic events, especially overnight.[7] In fact, existing WHO treatment guidelines recommend considering long-acting insulin analogues for individuals with diabetes who experience recurrent severe hypoglycaemia with human insulin.[27]

To address this evidence gap, we are conducting the Human vs Analogue Insulin for Youth with Type 1 Diabetes in Low-Resource Settings (HumAn-1) randomised controlled trial (RCT). Set in Bangladesh and Tanzania, this study aims to generate high-quality evidence to determine whether higher-cost long-acting analogue insulin reduces the risk of serious hypoglycaemia and/or improves glycaemic time-in-range (TIR) compared with human basal insulin regimens. We are also measuring quality of life (QOL), qualitative experiences and cost-effectiveness analyses to assist policy makers and payers with insulin coverage and procurement decisions in lower-resourced settings. This paper outlines the design and rationale of the HumAn-1 trial.

METHODS AND ANALYSIS

Clinical trial sites and partnerships

The HumAn-1 trial is enrolling 400 participants aged 7–25 years with T1D from Dhaka, Bangladesh (n=250) and Mwanza, Tanzania (n=150). This study was developed in collaboration with Life for a Child (LFAC),[28] a humanitarian organisation that supports young people with T1D in 48 countries. We selected Bangladesh and Tanzania as clinical trial sites as both are low-income countries with access and care challenges related to T1D, and LFAC has relationships with clinicians and centres in these countries. Implementation of the study was designed with input from the Tanzanian Diabetes Association and the Diabetic Association of Bangladesh. Enrolment distribution was chosen pragmatically and to include diverse geographic representation. A sample size of 250 participants in Bangladesh was chosen due to its larger clinic size; the remaining sample of 150 participants was designated for Tanzania because of its comparatively smaller patient population.

Participant recruitment and screening

Individuals with T1D, and their parents/guardians if under 18 years old, will be approached by local study staff or referred by their physicians as they present for routine diabetes care at each trial site. We use a convenience sampling approach as it best mimics real-world clinical practice and was easiest to operationalise. In Bangladesh, study enrolment began on 1 March 2023, and all study procedures are expected to finish by November 2024. In Tanzania, enrolment began on 11 July 2023 and is projected to end in February 2025. The full trial protocol can be found in the online supplemental file.

Participant eligibility

1. Inclusion criteria
   1. Children and young adults aged 7–25 years.
   2. Clinical diagnosis of T1D.
2. Exclusion criteria
   1. Prior use of insulin analogues.
   2. Individuals (or parents for children <18 years old) who refuse to or cannot provide informed consent.
   3. Individuals who are currently pregnant or plan to become pregnant over the next year.
   4. Previous use of a continuous glucose monitor (CGM) for glucose monitoring.
   5. Diabetes diagnosis within the past 12 months.
   6. Diagnosis of severe malnutrition.

Baseline assessment

After informed consent, participants will undergo a baseline assessment which includes collection of demographic information, vital signs, medical history and laboratory tests (figure 1). These laboratory tests will include

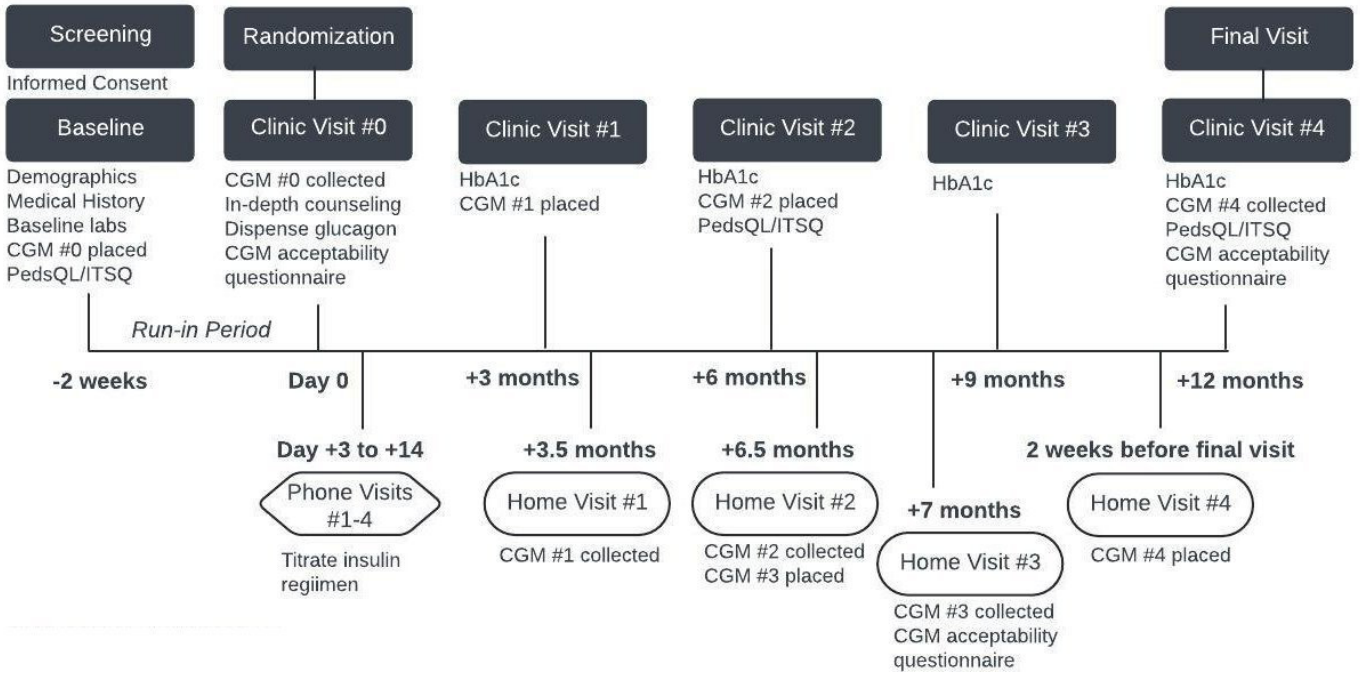

Figure 1 HumAn-1 study schedule of visits and activities. CGM, continuous glucose monitor; HbA1c, haemoglobin A1c; PedsQL, Pediatric Quality of Life Inventory; ITSQ, Insulin Treatment Satisfaction Questionnaire.

a blood glucose level, haemoglobin A1c (HbA1c), C-peptide, complete blood count, basic metabolic panel, liver panel, thyroid stimulating hormone, lipid panel, urine albumin-to-creatinine ratio and if applicable, a pregnancy test. They will also complete the validated quality of life (QOL) instruments Pediatric Quality of Life Inventory (PedsQL) 3.2 Diabetes Module and the Insulin Treatment Satisfaction Questionnaire (ITSQ).[29 30]

Continuous glucose monitors

Blinded CGM sensors (FreeStyle Libre Pro IQ; Abbott) will be placed five times on every study participant: baseline visit (CGM #0), 3-month clinic visit (CGM #1), 6-month clinic visit (CGM #2), 6.5-month home visit (CGM #3) and 2 weeks prior to the final, 12-month clinic visit (CGM #4) (figure 1). After 14 days, a study staff member will download the sensor data and remove the sensor. CGM #0 and CGM #4 will be removed at the clinic. CGM #1, CGM #2 and CGM #3 will be removed at home visits. CGMs #2 and #3 will collect primary outcome data back-to-back, designed in part for redundancy, in the case that one CGM fails to record data or prematurely falls off the body. The CGM at 6.5 months (CGM #3) will be placed for all participants, unrelated to the results of the 6-month CGM (CGM #2). To ensure that glycaemic changes are not due to CGM access, all sensor data will be blinded to participants, treating clinicians, site investigators and the principal investigator (PI). Participants will have the opportunity to review a copy of their CGM data at the conclusion of the study.

Randomisation procedure

Randomisation is stratified by centre to account for differences in the patient population and clinical practice patterns that may affect study outcomes. The 1:1 randomisation sequence was prepared in advance using the 'blockrand' package in R statistical software (V.4.2.2). The unblinded statistician from the university data centre team created the randomisation sequence, which was done independently of the blinded statistician conducting the primary analyses. Local trial staff will use the online data management system developed for this trial to obtain the next randomisation sequence. Neither the PI nor the local trial staff will have access to the randomisation sequence. Treatment assignment will only occur after a study participant has met all eligibility criteria and completed the baseline study procedures during the run-in phase.

Control group

Participants randomly assigned to usual care will continue their baseline human insulin regimens, which include either NPH (Insulatard; Novo Nordisk or Humulin N; Eli Lilly) with regular insulin (Actrapid; Novo Nordisk or Humulin R; Eli Lilly) or premixed (70/30) (Mixtard 30; Novo Nordisk or Humulin M3; Eli Lilly) insulin alone or with regular insulin. Doses of insulin will be adjusted individually at the discretion of the treating clinician.

Intervention group

In the intervention group, participants will be randomised to once daily biosimilar insulin glargine (Basaglar; Eli Lilly). At randomisation, the site physician will review each participant's medical record to determine the glargine starting dose, which is generally equal to 80% of their total basal human insulin dose prior to switching (per International Society for Paediatric and Adolescent Diabetes guidelines and a switching guide developed

by LFAC).[31] Glargine doses are typically administered once daily at bedtime, but may be given two times per day and will be adjusted at the discretion of the treating clinician. The LFAC and Changing Diabetes in Children programmes will donate all the insulins, glucometers and test strips used in the study.[28 32]

Education, insulin titration and glucagon

After randomisation, all participants will enter a 2-week insulin titration phase (figure 1). During this phase, participants randomly assigned to human insulin will continue their usual care; however, they will receive the same frequency of blood glucose testing and the same intensity of education and counselling as those randomised to glargine (eg, four phone visits every 3 days for 2 weeks following randomisation). Participants in both groups will have equal access to test strips (sufficient to test up to five times per day during the active titration phase and three times per day thereafter). Both treatment arms will subsequently titrate their assigned basal insulin dosage according to a fasting glucose target set according to local practice patterns. We will not recommend aggressive lowering of fasting glucose levels or HbA1c because prior studies show that the rate of severe hypoglycaemia is common in these settings. All participants will receive either intranasal glucagon (Baqsimi; Eli Lilly) or auto-injector glucagon (Gvoke HypoPen; Xeris Biopharma) to be used as a rescue medication for severe or life-threatening hypoglycaemia.

Outcome measures

Our two co-primary outcomes are: (1) per cent time-in-serious-hypoglycaemia (<54 mg/dL) and (2) per cent time-in-range (70–180 mg/dL). Both will be recorded as continuous variables ranging from 0% (no time) to 100% (all time) as measured by CGM data collected at the 6-month and 6.5-month visits (CGMs #2 and #3) for each participant. We selected these co-primary outcomes after consulting international experts and reviewing global consensus guidelines for T1D.[33] While level 2 hypoglycaemic events (<54 mg/dL) are less common than milder level 1 events (<70 mg/dL), they are far more likely to be clinically significant.[5] Durable increases in TIR are strongly associated with improved glycaemic control and an associated reduction in the risk of microvascular complications of T1D.

Secondary outcomes include time-in-hypoglycaemia (<70 mg/dL); time-above-range (either >180 mg/dL or >250 mg/dL); number of nocturnal hypoglycaemic events (<70 mg/dL during 24:00–06:00 hour) as measured by CGM data collected at the 6-month (CGM #2), 6.5-month (CGM #3) and 2 weeks prior to 12-month (CGM #4) visits; HbA1c collected at 6 and 12 months; rate of severe hypoglycaemic events (requiring external assistance for recovery); rate of symptomatic hypoglycaemic events reported by clinical history; rate of diabetic ketoacidosis (measured by self-report and confirmed through review of hospital records) and all-cause mortality through the 7-month visit (when CGM #3 results are collected) and up to the 12-month visit. We will also explore durability of treatment effects by comparing the percentage of time <54 mg/dL and TIR during the final 2 weeks of the 12-month follow-up period.

Adverse event (AE) monitoring process

Study personnel will be available via a dedicated study phone number (or via SMS) should hypoglycaemia or other adverse events (AEs) occur. All serious adverse events or unanticipated problems will be reported to the independent Data and Safety Monitoring Board (DSMB) within 7 days of notification of the event.

Data management

In collaboration with our international partners, the Centre for Biostatistics and Qualitative Methodology (CBQM) at the University of Pittsburgh helped develop a web-based electronic data management system specifically for this study. The password-protected and encrypted system, accessible from any computer with internet access, guides study staff through recruitment and informed consent procedures, randomisation and study interventions. The electronic system will also be used to securely record and transmit trial data (endpoints, safety events) from local sites to the CBQM.[34] Personal identifiers will be visible to local site staff but are deidentified in the data management system and not available to the PI or other study staff.

Power and sample size

We estimated power using a bootstrap-resampling approach due to possible non-standard distribution of the primary outcome variables. Using individual participant CGM data from a pilot study of over 80 children with T1D in Uganda and Kenya (personal communication Professor Antoinette Moran, University of Minnesota), we calculated a mean per cent time <54 mg/dL of 5.8%, SD of 6.6 and maximum time <54 mg/dL of 24%.[35] We assumed a clinically meaningful 33% relative reduction in per cent time-in-serious-hypoglycaemia (eg, from a median of 6% to 4%) as clinical guidelines target <15 min per day (~1%) at <54 mg/dL. In each simulated trial, the usual-care arm had an outcome from the 'control' distribution, while the glargine arm had an outcome from the control distribution multiplied by 0.67, corresponding to a 33% relative reduction in time-in-serious-hypoglycaemia.

To estimate the study power, we simulated outcomes for the control group (human insulin) and treatment group (analogue insulin) at sample sizes ranging from 100 to 400 participants, performing planned primary analyses on simulated datasets. The power to detect a treatment benefit of glargine was computed as the percentage of simulated trials with a p value <0.025 favouring glargine on each of the co-primary outcomes to control the overall trial-wide type 1 error rate of 0.05. With an estimated 25% lost to follow-up, an analytic sample size of 300 participants (150 per arm) has 78% power to detect a 33%

relative reduction in time-in-serious-hypoglycaemia. If the benefit is larger (eg, 50% relative reduction), there will be over 99% power to detect a treatment benefit.

For the time-in-range endpoint, we used an absolute increase due to the distribution, with a mean time-in-range of 27% (SD=17) from the pilot data. A 10% absolute increase in time-in-range was considered clinically meaningful.[36–39] A sample size of 400 accounting for a 25% dropout rate to equal 300 provides >99% power. Our analytic strategy allows the trial to be positive if glargine benefits either the time-in-serious-hypoglycaemia or the time-in-range endpoint.

Statistical analysis

For each co-primary endpoint, per cent time-in-serious hypoglycaemia and per cent time-in-range, data will be averaged across both sensors collected during the intensive CGM phase (month+6 to +7) to compute a single value for each participant. The primary analysis for each endpoint will use a multivariable linear regression model where treatment assignment is the primary fixed effect of interest with age, study site and time-in-serious-hypoglycaemia or time-in-range from the baseline CGM (run-in phase, prior to initiation of study treatment), respectively, for each endpoint, included as covariates. This approach increases statistical power by adjusting for baseline covariates strongly associated with the outcome and provides a safeguard against random imbalances in the baseline risk of hypoglycaemia. In the primary analysis, we will include all available sensor data regardless of the duration of sensor wear or the number of days of glucose measurements. A sensitivity analysis will include only sensors with at least 70% of data availability during each 14-day wear period (ie, ≥9.8 days).

We will perform additional sensitivity analyses. The first will be multiple imputation analysis, imputing missing outcome data based on observed baseline data. The second will be a win-ratio analysis, ranking participants based on outcomes: those who died (worst outcome), those who discontinued due to an AE (second worst), those who discontinued without an AE (third worst) and those with complete CGM data ranked by per cent time-in-serious-hypoglycaemia, with higher scores representing worse outcomes. This approach provides an estimate of which treatment arm led to better overall outcomes, including death, discontinuation and hypoglycaemia in a single composite outcome measure.

There are no planned interim analyses testing for efficacy or futility; by the time a sufficient number of participants complete follow-up to perform such analyses, the trial will be almost fully enrolled. Data on enrolment, progress during the trial and safety are being reported to the DSMB every 6 months to help monitor for any safety concerns. There are no prespecified stopping triggers, but the DSMB has leeway to recommend a pause in enrolment if they judge a preponderance of safety events in one arm warrant closer examination.

Substudies

The HumAn-1 trial includes several substudies: QOL, qualitative and cost-effectiveness analyses. Detailed methods for these substudies will be discussed in forthcoming manuscripts.

QOL substudy

QOL measures provide valuable insight into participant experiences and can be predictive of clinical outcomes. Data will be collected at recruitment, at 6 months after randomisation and at 12 months after randomisation using the PedsQL 3.2 Diabetes Module (Child Report for ages 8–12) and the ITSQ.[29 30] Both tools were translated and linguistically validated by the study team for use in Tanzania and Bangladesh. Study staff members will orally administer questionnaires to participants in their preferred language and responses are entered electronically by staff. The Child Report for ages 8–12 of the PedsQL will be used for all study participants. All trial participants will be at least 7 years of age when enrolled. Local study staff in Bangladesh and Tanzania determined the translated age-specific forms to be very similar and that all participants aged 7 to 25 would understand the Child Report for ages 8–12. To mitigate any potential comprehension issues, children under age 12 will be permitted to have a caregiver present for administration of the tools, and parents will be permitted to support their child in providing responses. For older children, the caregivers will not be present. By measuring QOL and treatment satisfaction at three time points in both arms using standardised tools, we aim to understand the change in QOL and treatment satisfaction in each arm over time. We will also capture participant feedback on the acceptability of CGM devices using a questionnaire that was developed for this study. The CGM questionnaire will be administered at baseline and after the 6-month and 12-month CGM removal.

Qualitative substudy

The qualitative study is being led by a team from the London School of Hygiene & Tropical Medicine and consists of over 120 semistructured interviews in two phases: exploratory (before the trial data collection begins) and explanatory (after the start of the trial from September 2023 to January 2025). Interviews with participants, caregivers, health workers and stakeholders aim to learn about experiences of living with T1D in resource-constrained settings and of taking part in the trial in each study setting. It may help explain the quantitative study findings and provide practical implementation lessons. Different participants and caregivers will be interviewed for the two phases. The exploratory phase population will be sampled from the clinic population and may not necessarily be enrolled in the trial. For the explanatory phase, patients and caregivers will be selected by a combination of convenience and purposive sampling of those attending the clinic for their RCT follow-up appointments. Children will be given the option of having their

caregiver outside the room or in the room with them. For safeguarding, if the parents are outside the room, a second research team member will accompany the children in the room during the interview. Interviews will be conducted in Bangla and Swahili by trained local staff in Bangladesh and Tanzania. Following translation into English, the qualitative study teams will analyse the findings using a combination of inductive and deductive approaches.

Cost-effectiveness substudy

The cost-effectiveness substudy, led by the Clinton Health Access Initiative, will assess the cost-effectiveness of long-acting insulin analogues versus intermediate-acting human insulins in a real-world resource-limited setting. Trial results (eg, the rate of severe hypoglycaemic events, hospitalisation rates) will be used to inform the economic analyses. Specifically, we aim to use trial-derived differential treatment effects to estimate the health systems cost per quality-adjusted life year gained in each arm.

Patient and public involvement

Local study staff, including the site investigators, were regularly consulted throughout the protocol development process to ensure the appropriateness of data collection instruments. They advised on site-specific, culturally appropriate approaches. For example, local staff in Bangladesh advised that pregnancy tests performed on unmarried females would be perceived as culturally offensive; therefore, baseline pregnancy tests will only be performed for married participants.

Before participant recruitment begins, we will hold in-person meetings with stakeholders, including hospital and health centre leadership, clinical staff, regional medical officers, participants and caregivers. These meetings will provide an opportunity for stakeholders to learn about the study and ask questions. Local study staff maintain close contact with participants and regularly inform the primary study team about any concerns related to the study.

Ethics and dissemination

This study was reviewed and approved on 8 February 2022 by the Institutional Review Board at the University of Pittsburgh (STUDY21110122). It has also been approved by the National Health Research Ethics Committee at the National Institute for Medical Research in Tanzania (NIMR/HQ/R.8a/Vol.IX/4265) and the Ethical Review Committee (ERC) of the Diabetic Association of Bangladesh (BADAS-ERC/EC/22/405).

The consent process will take place in a private room at the clinic where study participants receive routine clinical care. Consent will be obtained and documented after it has been determined that the potential study subject meets inclusion and exclusion criteria, and prior to conducting any research activities or study procedures (eg, baseline survey, randomisation, CGM sensor placement). Study participants will be assured that their decision to participate or not in the study is voluntary and will not affect their clinical care or their relationship with their care providers or hospital.

Study staff obtaining consent will provide ample time for participants and their caregivers to ask questions and voice concerns about the study in their local language. Contact information of local study staff (ie, a phone number to call) will be provided to participants in case they have questions at a later point. Participants will be informed that they may withdraw consent at any time and withdraw from the study without any consequence to their relationship with their routine clinical care providers. Verbal assent will also be sought before performing research procedures at every visit (eg, downloading data from a CGM sensor). All consent/assent forms and signatures will be collected electronically.

Study findings will be presented at international academic and policy-oriented conferences, and manuscripts of study findings will be published in peer-reviewed journals.

DISCUSSION

The HumAn-1 trial will provide valuable insight into the clinical impacts of long-acting insulin analogues compared with intermediate-acting human insulin for T1D youth in understudied low-resource settings. The unique circumstances faced by individuals with T1D, such as food insecurity, limited healthcare access, constrained medication/testing supplies and context-specific medical comorbidities such as malaria-induced hypoglycaemia, may not be represented by existing studies. Using CGMs to demonstrate the comparative clinical benefits of analogue insulins for patients living with T1D in low-income countries could inform clinical guidelines and improve drug procurement decisions in these settings. This is a topic that requires urgent attention, as T1D cases are expected to increase by up to 116% by 2040 compared with 2020, with the largest relative increases expected in low- and middle-income countries.[4] By addressing these data gaps and providing evidence that may shape best practices in these settings, we hope to improve T1D care globally, especially for those facing the greatest barriers to care.

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Contributors JL is the guarantor. SK, BLR, C-CHC, GO, EA, MLP, BZ, KR and JL: design and concept, acquisition, analysis or interpretation of data and critical revision of the manuscript for intellectual content. AF, CJ and CL: acquisition, analysis or interpretation of data, critical revision of the manuscript for intellectual content, drafting of the manuscript and critical revision of the manuscript for intellectual content. S-RC: drafting of the manuscript and critical revision of the manuscript for intellectual content. All authors read and approved the final manuscript.

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