Statistical Analysis Plan (SAP)

Continuous Glucose Monitoring in Prediabetes (G1)

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List of Abbreviations

AGP - Ambulatory Glucose Profile

BMI - Body Mass Index

CGM - Continuous Glucose Monitoring

CTSA - Clinical and Translational Sciences Institute

IPAQ - International Physical Activity Questionnaire

LME - Linear Mixed-Effects Model

LQMM - Linear Quantile Mixed Model

MAR - Missing at Random

MCAR - Missing Completely at Random

REDCap - Research Electronic Data Capture

SAP - Statistical Analysis Plan

1. Introduction

This document outlines the proposed analyses for Continuous Glucose Monitoring in Prediabetes (G1) study evaluating continuous glucose monitoring (CGM)-derived glycemic metrics among adults with prediabetes or prediabetes risk. The study employs a within-subject design without CGM masking, allowing for continuous measurement of glycemic variability while participants receive real-time glucose feedback at five-minute intervals via a smartphone application during CGM wear.

The purpose of this document is to describe the statistical analysis plan (SAP) for this study, including definitions of analysis populations, outcome measures, study time points, and planned statistical methods for summarizing CGM-derived outcomes and participant-reported narrative data.

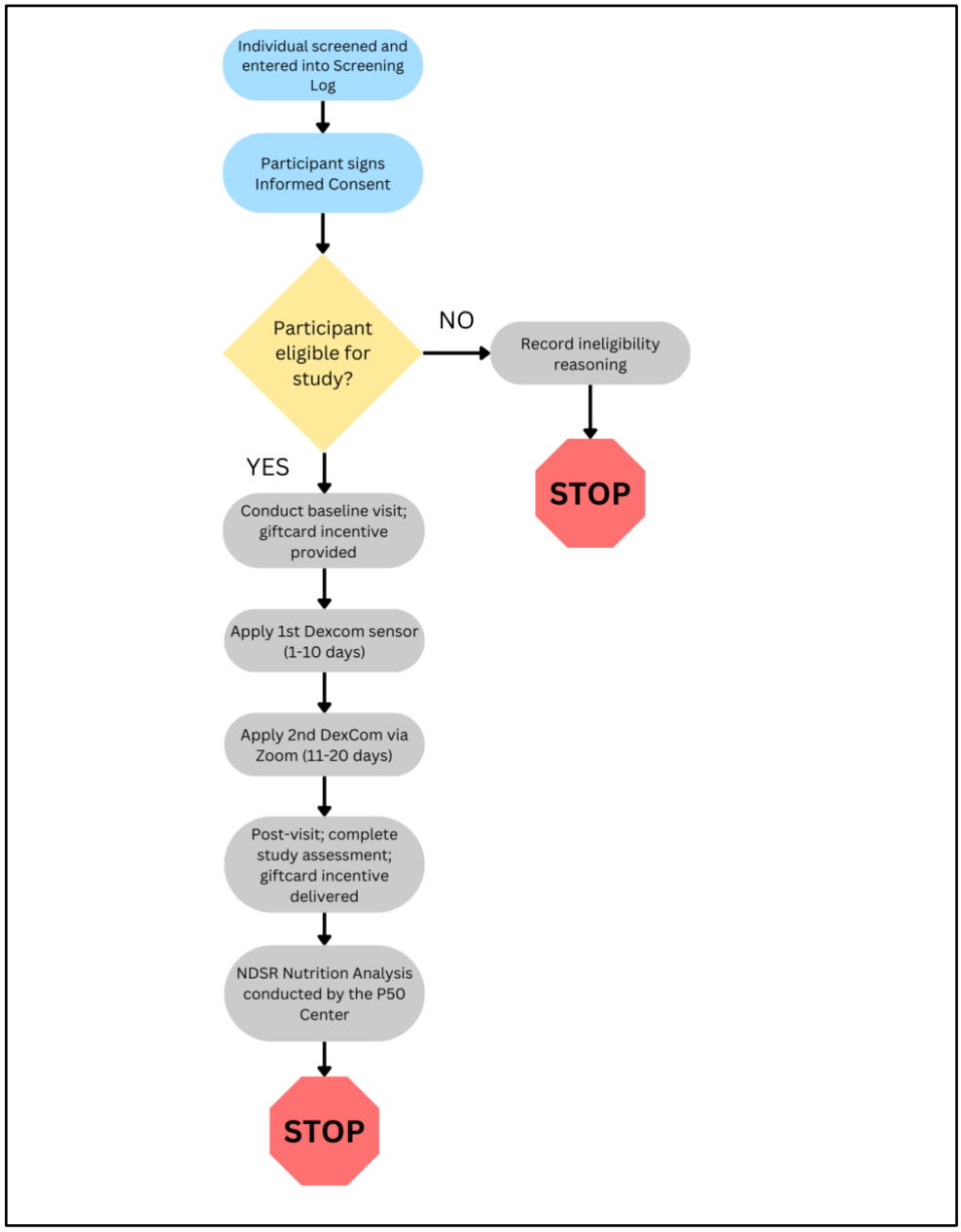
2. Study Design

Study employs a within-subject design without CGM masking, enabling the measurement of glycemic variability, where participants receive feedback every 5 minutes while wearing the CGM device. This is an observational study where participant glycemic data is observed when CGM feedback is available on their smartphone app. This design captures continuous baseline values on the primary study outcome across 20 consecutive days while recorded video-based narratives are provided by participants each day as well as during the structured interview.

Glycemic variability. The primary outcome measure for the project is glycemic variability, which will be assessed using CGM automated data capture and the Dexcom Clarity cloud. We will utilize the Dexcom G6 Pro system (https://provider.dexcom.com/products/dexcom-g6-pro/training-resources) to capture glycemic variability over 14-20 complete wear days, with data recorded automatically every five minutes and timestamped. Participants will change the transmitter once on day 10, as the sensor has a wear time of 10 days. Data will be transferred to the Clarity cloud using an external Dexcom reader. Subsequently, the Clarity file will be exported and sent to the statistician for processing in RC software, where all variables for the complete ambulatory glucose profile (AGP) panel for glycemic variability will be calculated. Our main outcome analyses will focus on key variables related to glycemic control. Additionally, CGM data will allow us to generate important covariates, such as the % time worn by each participant per week and the number of times a participant changed the CGM sensor.

The study consists of four sequential timepoints. At baseline, participants complete an initial assessment prior to device use. Participants then wear a CGM sensor for a 10-day period (Phase A). At the end of the first wear period, the sensor is replaced per manufacturer instructions, followed by an additional 10-day CGM wear period (Phase B). Upon completion of the second wear period, participants complete a post-study assessment visit.

Figure 1 Flowchart of screening and inclusion process



*NDSR was collected for P50 center-level analyses.

2.1. Sample size calculation

This was a single-arm pre-post study. Consistent with recommendations for pilot studies, a sample size of 20 participants was chosen to assess feasibility and estimate outcome variability (i.e., to characterize typical ranges and within-person variability and to assess data completeness/quality) rather than to formally test hypotheses[12]. With limited prior data for this exact population and protocol, the most informative use of the pilot sample was to obtain preliminary estimates (means, SDs, and within-person variability) with enough data density

per participant to support planning. Sample size considerations were also informed by principles of data saturation commonly applied in qualitative research[3]. These pilot-derived variance components were then intended to inform a powered sample size calculation for the subsequent study designed to test intervention effects on CGM outcomes.

3. Aims and Objectives

Aim 1: To determine whether wearable CGM with smartphone feedback can improve glycemic control among individuals with prediabetes or prediabetes risk.

4. Demographics and Baseline Assessments

The following are specific demographic / baseline assessments of interest for analyses.

1) Age
2) Sex
3) Ethnicity (NIH/OMB)
4) Race (NIH/OMB)
6) Highest level of education
7) Current employment status
8) Total household income
9) Health insurance
10) CDC prediabetes risk score
11) Body Mass Index (BMI)
12) Physical Activity Level (International Physical Activity Questionnaire [IPAQ])
13) Finger prick HbA1c (%)
14) Self-reported history of prediabetes

5. Data Storage

Data will be collected and managed using Research Electronic Data Capture (REDCap) housed at University of Southern California's Clinical and Translational Sciences Institute (CTSI) and Dexcom Clarity[4]. REDCap is a secure, web-based application designed for research studies that provides an intuitive interface for validated data entry, audit trails for tracking data manipulation and export procedures, and automated export procedures for seamless data downloads to common statistical packages, and procedures for importing data from external sources.

6. Outcomes

6.1. Primary outcome

Change in mean glucose (mg/dL) from baseline. Mean glucose will be derived from CGM data obtained from the Dexcom Clarity system. Raw glucose values will be processed and analyzed using the R statistical software package *iglu*[5] to generate the full CGM variability metrics panel. For each participant, mean glucose will be calculated as the average of all valid CGM glucose readings within each 10-day assessment period. The outcome measure represents the change in mean glucose between the baseline 10-day assessment period and the subsequent 10-day period.

6.2. Other pre-specified outcome

Videos obtained from informal and semi-structured interviews (total minutes).

6.3. Safety outcomes

Adverse events

Adverse events are reported by participants or occasional assessment.

7. Analytic Dataset

Primary analyses will include participants with sufficient CGM data; inclusion required at least 2 days of valid CGM data within each 10-day assessment period. Descriptive analyses for other pre-specified outcome will include all participants that provided at least 1 video.

8. Statistical Analyses

8.1. Analytic oversight and preprocessing.

Descriptive statistics will summarize participant characteristics and outcomes (means ± SD or medians [IQR]; proportions for categorical variables). Prior to modeling, distributions will be visualized to assess skewness/kurtosis; influential points will be evaluated (Cook's distance, DFBETAs) and addressed via winsorization or removal with justification. Outlier handling decisions will be documented a priori in the analysis plan. For CGM variable generation**,** raw 5-minute glucose values (excluding Day-1, replacement, and removal days to minimize calibration/transition artifacts) will be used for visualization (daily traces; AGP-style plots) and processed with the *iglu* R package to derive standardized metrics.

8.2. Primary outcome.

For the primary outcome of mean glucose (mg/dL), we will first perform a Wilcoxon signed-rank test to compare paired mean glucose values between Phase A and Phase B, and then fit a linear mixed-effects model (LME) to estimate within-person change from Phase A to Phase B while accounting for repeated measures: $Y_{ij} = \beta_0 + \beta_1(\text{Baseline } Y_i) + \beta_2(\text{Phase})_j + \eta_i + \varepsilon_{ij}$ where η_i is a participant-level random intercept and Phase is categorical (A vs B). If assumptions are not met (e.g., skewed residuals), we will fit a linear quantile mixed model (LQMM) as a robust alternative. Candidate covariates (pre-specified) include baseline age, sex, and BMI. Note that additional exploratory analyses may be conducted to examine other demographic variables and baseline characteristics as covariates by assessing their potential associations with CGM outcomes. Variance inflation factors will be examined to rule out multicollinearity. Results will be reported as model-based estimates, corresponding 95% confidence limits, and p-value of the corresponding hypothesis test. All analyses will be performed in R (≥4.5.1).

8.3. Other pre-specified outcome

Descriptive statistics will be used to summarize the total minutes of videos captured and processed. For each participant, the total duration of videos will be calculated, and the following summary measures will be reported: number of participants with video data and mean ± SD or median [IQR] total minutes of videos captured and processed.

9. Missing Data

Missingness will be characterized (MCAR/MAR) and addressed using likelihood-based methods and, if needed, multiple imputation or inverse probability weighting; sensitivity analyses will compare approaches.

References:

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