Libre 2 CGM plus Glycemic Excursion MInIMization (GEM) in the Treatment of PrEDiabetEs: The IMPEDE Study

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Approval:

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 LIST OF ACRONYMS

AE	Adverse Event
A1C	Hemoglobin A1c
AUC	Area Under the Curve
BMI	Body Mass Index
BG	Blood Glucose
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitor
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CU	University of Colorado
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEM	Glycemic Excursion Minimization
HIPAA	Health Insurance Portability and Accountability Act
HSR	Health Sciences Research
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MRN	Medical Record Number
NCT	National Clinical Trial
PI	Principal Investigator

PPG	Postprandial Glucose
SAE	Serious Adverse Event
SMBG	Self Monitoring Blood Glucose
SOA	Schedule of Activities
SOC	Standard of Care
T2D	Type 2 Diabetes

2 PROTOCOL SUMMARY

Title	**Libre 2 CGM plus glycemic excursion mIniMization (GEM) in the treatment of PrEDiabEtes: The IMPEDE Study**
Funding Organization	Abbott
Site	University of Colorado
Study Design	2 between (groups) x 2 within (pre-post) partial cross-over randomized clinical trial
Study Description	For people with prediabetes, it may be possible to delay or prevent the progression to diabetes by reducing postprandial glucose (PPG). Our Glycemic Excursion Minimization (GEM) lifestyle intervention guide can reduce PPG in people with type 2 diabetes and has been studied in this population with continuous glucose monitor (CGM) feedback to help the user learn what elevates and lowers their PPG. This study examines if the GEM lifestyle intervention guide plus continuous feedback from the Libre 2 CGM will allow participants with prediabetes with A1c 6.0-6.4 to (1) improve their metabolic status by illustrating the effects of their routine food and physical activity choices on their glucose levels and variability, more than Routine Care (RC), and (2) to enhance these investigations by adding comprehensive plasma proteomics to the analyses. We will recruit up to 70 adult participants with prediabetes through the University of Colorado, with the goal of having at least 30 participants complete the study. Participants will be randomized to the intervention or RC. Those randomized to the intervention will be given a GEM treatment manual, Libre2 CGM, and an activity monitor and will follow the GEM lifestyle intervention guide for 4 months. Those participants randomized to RC will follow recommendations from their primary care provider. RC participants will have the opportunity to receive GEM four months after consenting and completing the RC pre-post assessments. It is anticipated that 50% of the RC participants will want/be able to cross over to GEM upon completion of RC. Pre-post blinded CGM data and activity data, clinical, and psychosocial outcomes will be collected and analyzed. We anticipate this pilot project will demonstrate the benefits of using GEM plus Libre 2 to reduce percentage of CGM readings>120, from blinded pre-post LibrePro, as well as reduce BMI and depressive symptoms and increase modified diabetes empowerment. Comprehensive proteomics will be measured on small samples of EDTA treated venous blood. Individual proteins and protein pathways will be measured for each of the participants.
Primary Objective	To determine if individuals with prediabetes can use GEM plus Libre CGM to improve metabolic control.

Primary Endpoints	Pre-post reduction in percentage of CGM readings > 120 from blinded pre-post LibrePro; additional outcomes of particular interest include, A1C and BG variability
Secondary Objectives	(1) To determine if individuals with prediabetes can use the GEM manual with Libre CGM to improve other clinical, psychosocial, and behavioral outcomes. (2) To explore psychological (readiness to change) and physiological (proteomics) measures. (3) To generate user feedback about improving the intervention.
Secondary Endpoints	(1) Endpoints will include psychosocial scales, basic demographic information, comparative labs, Steps, Hours Active, or Active Minutes. (2) Analysis of individual proteins and protein pathways measured through use of a multiplex proteomics platform. (3) Endpoint will include the Program Importance Questionnaire
Participation Criteria	Inclusion Criteria: • Age 25-70 years • A1C 6.0-6.4 • Documented diagnosis of prediabetes • Have a smart phone • Able to read English, as the GEM guide is currently only available in English • Willing and able to follow the study procedures as instructed Exclusion Criteria: • Diagnosis of diabetes mellitus • Currently taking any diabetes medication • Currently taking medication that promotes insulin resistance or otherwise interferes with metabolic control (e.g. prednisone) • Has a condition that precludes a low carbohydrate diet, such as gastroparesis • Has a physical or medical condition that precludes walking 120 steps per minute, for 10 minutes or longer • Has documented kidney disease that would preclude participation in study per PI discretion • Active or planned cancer treatment. • Extreme visual or hearing impairment that would impair ability to use real-time CGM • Pregnant or anticipates becoming pregnant in the next 4 months. • Anticipates moving within the next 4 months. • Treating physician, for any reason, considers their patient inappropriate for the study (e.g. uncontrolled bipolar disease)
Sample Size	Up to 70 screened participants with prediabetes and an A1c between 6.0-6.4 to provide a cohort of 36 enrolling in the trial, wth a goal of at least 30 participants completing the trial.
Description of Study Intervention	Blinded CGM data (obtained through the use of the Libre Pro) and blinded activity data (obtained through the use of a FitBit) will be obtained for 2 weeks on all participants at the start and end of the study, and baseline clinical data collection and psychosocial scales will be completed prior to randomization. The intervention group will be given Libre 2 supplies for 4 months, an activity monitor, and the 4-chapter GEM paper guide. The intervention group will complete a virtual or inperson study visit where they will receive instructions on how to apply their unblinded Freestyle Libre and connect it to the study account, as well as how to

	register their Fitbit to the study account. If the visit will be conducted remotely, participants will be mailed their CGM, Fitbit, and the GEM manual. Participants will receive one telephone call to review use of the GEM Guide and call at two weeks and six weeks later when the probability of dropouts from lifestyle intervention peaks. Participants will follow the self-directed GEM guide for 4 months (a 1-month treatment period followed by a 3-month maintenance period) while wearing a FitBit activity monitor and a Freestyle Libre 2 CGM. Participants will be given this guide and a study email so they can easily ask questions about the GEM program during treatment. Fielding GEM questions will help the study progress smoothly and will gain information that might improve the Guide in the future. Relevant questions and corresponding answers will be posted on a study website for all participants to review, if desired. However, all medical management questions will be referred back to the participant's treating physician.The GEM Guide for Prediabetes contains the following information in four chapters: Glucose Impact of Routine Choices, Recovering from BG Excursions, Reducing BG Excursions, and Maintenance. The RC group will follow recommendations from their primary care physicians and clinicians that will be tracked for later analysis. RC participants will have the opportunity to receive the intervention four months after consenting and completing of the RC pre-post assessments. Comprehensive proteomics analysis will be done at the same time after all samples have been collected.
Study Duration	This study will last approximately 24 months from the beginning of subject recruitment to data analysis.

3 INTRODUCTION

3.1 Background & Rationale

Diabetes represents a major national and global health problem. Eighty-eight million adults in the US and 352 million individuals worldwide have prediabetes, with 1.5 million Americans transitioning to diabetes annually.[1] Preventing or delaying this conversion from prediabetes to diabetes would be a major medical advance that could improve the health of many individuals and reduce health care costs.

Metformin is a frequently used but often suboptimal treatment for preventing the progression of prediabetes to diabetes. One study found that one third of patients initiating metformin discontinued use within one year, and less than half of all patients are adherent to metformin.[2] Some patients experience intolerable symptoms, and long-term use of metformin is associated with anemia and declining cognitive function.[3] [4] [5] [6] [7]

Intensive lifestyle interventions hold promise as cost-effective treatment for prediabetes.[8] Conventionally, this approach involves weight loss of at least 7% and at least 150 minutes a week of moderate to vigorous physical activity, with a recommended year-long intervention.[9] Weight loss and moderate to vigorous physical activity can both prevent, delay, and treat the progression of prediabetes to type 2 diabetes (T2D).[10] [11] However, weight-loss lifestyle interventions are inappropriate for lean individuals, unwanted by others, and unsuccessful or unsustainable for other patients.[12] [13]

3.2 Glycemic Excursion Minimization

We found that a lifestyle management of T2D that reduces glycemic excursions (area under the curve - AUC) is an effective alternative treatment of T2D.[14 15 16 17 18 19]Our NIH funded research demonstrates that Glycemic Excursion Minimization (GEM) guide is more effective than weight loss alone in lowering A1c, reducing BMI, decreasing cardiovascular risk, and improving psychological functioning. Moreover, the efficacy of GEM appears broadly applicable since it is unrelated to baseline demographic, psychological, or disease severity variables. Furthermore, GEM sustains these benefits over a 13-month follow-up and without needing an intervening maintenance program. Additionally, our recent Abbott study found that GEM combined with CGM significantly improves A1c, glucose area under the curve, weight, and psychological functioning of adults recently diagnosed with T2D, and achieves this benefit with less diabetes medication.[19] These observations provocatively raise the following question: Is GEM plus CGM similarly an effective means of preventing the progression of prediabetes to T2D?

GEM is an appealing therapeutic strategy. GEM involves: 1) educating patients regarding how their choices impact both their current and future blood glucose (BG) fluctuations, 2) empowering individuals to make choices in the timings, amounts, and types of foods that diminish BG elevations, and 3) choosing types, amounts, and timings of physical activities that hasten the recovery of BG excursions. This approach presumes accurate and timely feedback of BG status to: a) educate patients regarding the impact of their choices, b) activate patients to take appropriate action when BG excursions are beyond their desired goals, c) motivate patients to repeat choices that either diminish extreme BG excursions or correct undesired BG excursion status, and d) investigate new food and activity choices to evaluate how they impact their BG excursion status.

More investigation needs to be done to establish the importance of CGM in treating prediabetes. Yost et al's investigation of CGM and low carbohydrate diets of adults with prediabetes[20] suggested that CGM plus a low carbohydrate diet was acceptable to their sample, led to lower A1c, and reduced sense of vulnerability to developing diabetes. However, it had multiple limitations that will be addressed by our proposed study: briefly, the aforementioned article 1) only had 20 days of CGM, 2) did not have a routine care group to distinguish the effects of diagnosis and enrollment in a study on A1c, AUC, weight reduction, etc., 3) did not measure A1c before and after their intervention, 4) required three face-to-face and two telephone patient contacts, 5) employed a primary outcome that was satisfaction with CGM and low carbohydrate diets, and 6) had a subject sample that was narrow, requiring a BMI of >30. In addition, our study will include the combination of the GEM manual and CGM to actively teach subjects how to interpret, predict, and effect the CGM results which is hypothesized to be a more active and powerful behavioral modification.

Our proposed investigation addresses many of the aforementioned limitations by focusing on reducing AUC rather than weight or CGM time above 180. Thus, GEM targets reducing post prandial, as well as periodic post snack and drink, glucose excursions. Our approach would employ two groups (with no weight restriction) to identify the effects of participation in a study. Our primary outcome variable of reduction in AUC (reduced % CGM readings above 120) is more appropriate to our patient sample. GEM requires no face-to-face visits. In contrast to the above studies that use

CGM to educate either the patient or artificial intelligence, GEM uses CGM feedback to educate, motivate, activate, and investigate. Additionally, our proposed study will also allow us to explore two preliminary issues: Dr. Cox has developed the Treatment Optimization Scale that is intended to predict which patients are more likely to do better on medication or lifestyle intervention. We anticipate that individuals with a strong preference to actively engage in a lifestyle intervention will do better on CGM and in the GEM group. Additionally, we will begin to explore proteomics in the study population, as described below.

3.3 Proteomics

Measuring plasma proteome changes could further enhance the proposed observations and provide new opportunities for advancing the management of patients with prediabetes.[21] We also propose to sequentially (before, during crossover, and after treatment) measure and analyze the plasma proteome using SomaScan analyses of ~7,500 proteins on a small sample of heparinized plasma (~2cc). This preliminary analysis will begin to characterize the effects of our treatment approach on inflammatory, oxidative stress, and other plasma proteins and protein pathways that change during the evolution of pre-diabetes to diabetes. This data could suggest further testing of specific biomarkers that could be used in the future to guide or assess treatment strategies to perhaps identify responders and non-responders—a more personalized approach and one that ultimately might provide additional impetus for individuals to monitor their glucose levels using CGM and to adhere to treatments that improve their CGM assessments. A recent article (2021) in E BioMedicine emphasizes the importance of characterizing this patient population using comprehensive proteomic approaches.[22] Briefly, the authors discovered that: (a) a broad range of blood-borne proteins are altered at the very early stage of screening-detected T2D patients, and (b) that newly identified protein patterns reflect key metabolic syndrome features such as insulin resistance, fatty liver disease, hyperglycemia, and adiposity as well as other protein pathways associated with diabetes. In addition, and importantly, proteomic changes observed at baseline were significantly attenuated during metabolic improvement associated with metformin treatment. They lauded their proteomic approach for its potential to predict diabetic status with high accuracy from the protein signature and as a way to deliver improved and more individualized health care.

3.4 Risk / Benefit Assessment

We assess this trial as posing **no greater than minimal risk**.

4 OBJECTIVES

We will investigate whether providing CGM within a structured, self-directed and personalized program (GEM) will allow participants with prediabetes to improve their metabolic status by illustrating the effects of their routine food and

physical activity choices on their blood glucose levels and variability, more than Routine Care (RC). We will enhance these investigations by adding comprehensive plasma proteomics to the analyses.

4.1 Primary Objective

The primary outcome variable will be participants' pre-post reduction in percentage of CGM readings >120, from blinded pre-post LibrePro. This is most relevant since the goal of GEM is to reduce glucose excursions and since 13% of non-diabetic adults' CGM readings exceed 120.[23]

Our hypothesis is that participants assigned to the intervention group will achieve a greater pre-post reduction in percentage of CGM readings>120 than will the control group.

4.2 Secondary Objectives

- To assess the reduction in A1c and Libre Pro glucose variability[24]
- To assess reduction in BMI
- To assess reduction in cardiovascular risk defined by UKPDS[25] and the ASCVD risk[26]
- To assess improvement in psychological function as defined by improvement in empowerment, measured through a modified Diabetes Empowerment Scale[27], fewer depressive symptoms,[28] and a modified Diabetes Knowledge Scale
- To measure dietary habits using Carbohydrate Routine Consumption Scale[29]
- To obtain data exploring psychological measures determining "readiness to change" using the MATCH and Treatment Optimization Scale.
- To obtain data exploring physiological proteomics measures. This will be addressed by analyzing individual proteins and protein pathways measured through the use of a multiplex proteomics platform that has been used in other clinical trials to characterize differential mechanistic effects that may identify eventual responders from non-responders.
- To obtain program feedback using the Program Importance Questionnaire

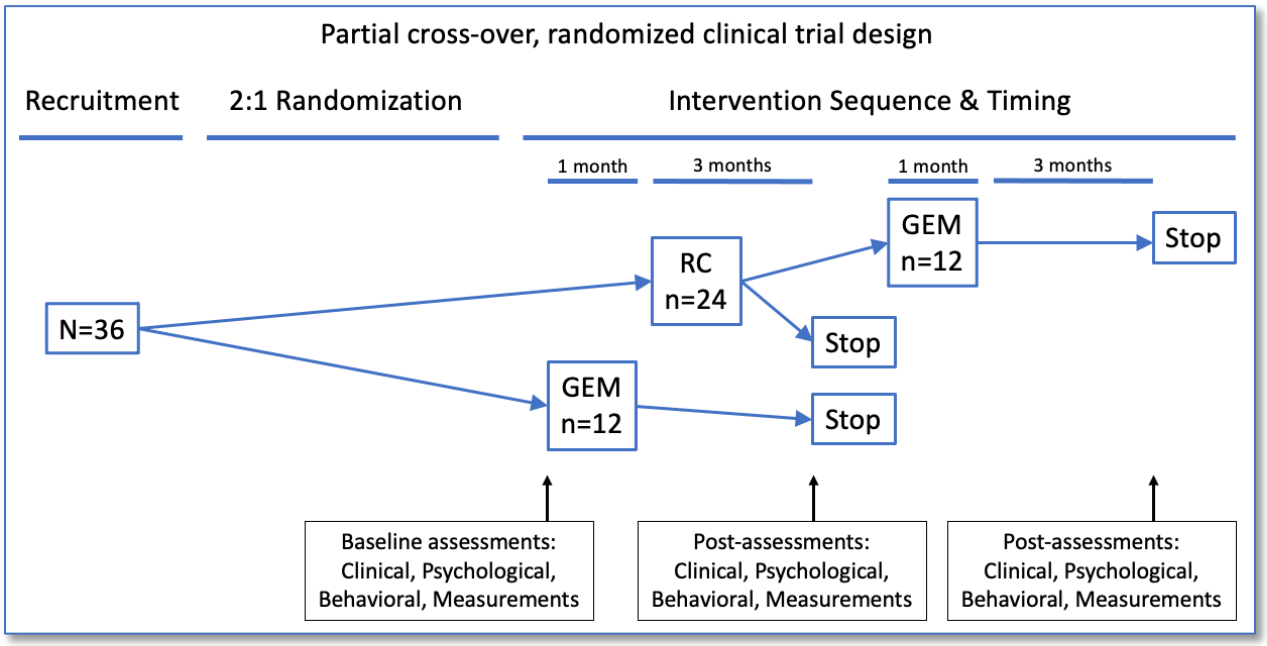
5 STUDY DESIGN

5.1 Study Overview

This is a single center, 2 between (groups) x 2 within (pre-post) partial cross-over randomized clinical trial. A total of up to 70 subjects will be enrolled to allow for screen failures and up to 20% anticipated attrition, with the goal of ending the study with 20 subjects completing the GEM intervention, including those who crossover from the routine care arm for a total of 30 subjects completed an arm and/or both arms. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study after informed consent.

Participants will be randomized to RC or GEM (2:1) where RC participants will have the opportunity to receive GEM four months after consenting and completion of the RC pre-post assessments. It was anticipated that 50% of the RC participants would want to and be able to cross over to GEM upon completion of RC.

However, 50% of our RC participants at post assessment did not qualify to cross over due to A1c being outside the 6.0-6.4 inclusion criteria range. This left less than 50% available to cross over to GEM, far fewer than anticipated. Given this reduced sample we will go from a 2:1 to a 1:1 randomization to RC. This allows allocating more participants directly assigned to GEM, thus relying less on RC crossovers. Given that this is a feasibility study and there were fewer participants that could cross over from RC to GEM due to post Routine Care A1c, the decision was made to change the randomization to 1:1. The investigator team felt this change was necessary in order to ensure that adequate data was collected from this feasibility study to power a larger study.



There will be 2 groups:

- Group 1. Routine Care (RC) participants will follow recommendations from their primary care providers. These recommendations will be tracked for later analyses.
- Group 2. GEM participants will be given Libre 2 supplies for 4.5 months, an activity monitor and the 4-chapter paper GEM guide which provides: 1) decisive didactic information about the effects of net carbohydrate consumption and routine physical activity on blood glucose fluctuations; 2) instructions to systematically use CGM feedback to educate them about how carbohydrates and physical activity impact their BG excursions, motivate them to repeat choices that lead to lower AUC, activate them to take steps to lower their BG elevations when detected by the high glucose alarm, and investigate the BG impact of new food and activity choices

concerning their effect on their BG; 3) employ structured self-monitoring (diary) to organize and identify personal patterns in their food and physical choices that impact their AUC; 4) GEM Supplement that provides additional information to the manual, e.g.frequently asked questions and answers, nutrient content of low glycemic load foods, case reports, youtube exercise videos; and 5) automated personalized daily text messages to "choose wisely" food and activity choices, and perform daily diary entries. The GEM manual for this prediabetes sample will follow the same format as that used with our diabetes sample: 1) become aware of metabolic costs of routine choices, 2) minimize BG elevations with personally relevant food choices, 3) hasten BG recovery with increased routine physical activity, and 4) plan for continuation of such lifestyle changes. The major adaptation in the GEM Guide for this prediabetes population focused on reducing risk of progression to diabetes and having to initiate diabetes medications. The GEM Guide was adapted based on clinical experience, the qualitative analyses of Yost et al,[20] and the literature on secondary prevention.[30]

Given that this is a pilot study, we did not perform a formal power analysis at this time because there are no data suggesting anticipated change in AUC for adults with prediabetes. However, 20 participants completing the GEM path through the study will provide data to estimate this effect size and therefore to enable power analysis for an anticipated follow-up NIH application. Additionally, N=15 was sufficient to find a pre-post effect in a previous study evaluating a different intervention in a prediabetes population.[20]

5.2 Criteria for evaluation

5.2.1 Data Collected

- Demographics (e.g., sex, age, race, smoking)
- Vital signs (e.g., height, weight, blood pressure)
- Lab tests (e.g.,A1c, lipids)
- FitBit data
- Psychosocial scales (e.g., Carbohydrate Routine Consumption Scale, MATCH scale, PHQ-8 depression scale)
- Comprehensive proteomics

5.2.2 Primary Endpoint

- pre-post reduction in percentage of CGM readings >120, from blinded pre-post LibrePro.

5.2.3 Secondary Endpoints

- reduction in A1c and Libre Pro BG variability
- reduction in BMI
- reduced cardiovascular risk defined by UKPDS and ASCVD risk calculator.
- improvement of psychological function as defined by a greater sense of modified diabetes empowerment, fewer depressive symptoms, and improved modified diabetes knowledge.

- To obtain data exploring psychological measures determining "readiness to change" using the MATCH scale, and Treatment Optimization Scale
- To obtain data exploring physiological proteomics measures. This will be addressed by analyzing individual proteins and protein pathways measured through the use of a multiplex proteomics platform that has been used in other clinical trials to characterize differential mechanistic effects that may identify eventual responders from non-responders.

5.2.4 Safety Endpoints

- Frequency of adverse events

6 PARTICIPANT SELECTION AND ENROLLMENT

6.1 Source of Participants

Subjects who meet the inclusion and exclusion criteria will be eligible for participation in this study following appropriate informed consent obtained from subject or subject's legal representative and written approval from their primary care provider. Since nearly all patients with prediabetes are treated in the primary care setting, participants will be recruited from primary care practices in the University of Colorado network, as well as through advertisement on websites, emails, social media, and other IRB approved modalities. Individuals generally will be recruited from the site's existing patient population or from a pool of individuals who contact the site. IRB requirements regarding recruitment materials and policies will be adhered to. Study recruitment methods may consist of the following:

- Use of Health Data Compass/TriNetX
- Culling of pre-existing databases of patients who have expressed interest in research participation. Those identified will be contacted via IRB-approved mailing sent through post, email blast, or via phone and will be provided information about how to complete the consent process and demographics survey;
- Support groups, patient education classes, and not-for-profit community support groups;
- IRB-approved paper and digital advertisements, brochures, postcards, flyers, and/or newsprint advertisements;
- IRB-approved digital advertisements posted on social media sites like LinkedIn, Twitter, YouTube, Instagram, Facebook, and other public forums managed by a clinical trial site;
- In-person recruitment and telephone recruitment by individual clinical sites; and
- An IRB-approved website dedicated to clinical trial recruitment.
- Letters/Emails to, phone calls with, or visits with area physicians informing them of the study and asking them to refer any eligible patients who might be interested

All recruitment methods and specific advertising materials will be IRB approved prior to their implementation. No individuals will be excluded based on gender or race. An equal gender distribution is anticipated.

6.2 Number of Participants

A total of up to 70 participants, with 20-24 anticipated to complete GEM due to trial design anticipating 50% of RC participants will want/be able to cross over to the intervention group and eligibility criteria.

6.3 Inclusion Criteria

- Adults between the ages of 25-70
- A1C of 6.0-6.4
- Documented diagnosis of prediabetes
- Have a smart phone
- Read English, as GEM currently only available in English
- Willing and able to follow the study procedures as instructed
- Having written approval by primary care provider

6.4 Exclusion Criteria

- Diagnosis of diabetes mellitus
- Currently taking any diabetes medication
- Currently taking a chronic medication that would interfere with metabolic control, such as prednisone
- Has a condition that precludes a low carbohydrate diet, such as gastroparesis
- Has a physical or medical condition that precludes walking 120 steps per minute, for 10 minutes or longer.
- Has kidney disease.
- Active or planned cancer treatment.
- Those who cannot speak English.
- Extreme visual or hearing impairment that would impair ability to use real-time CGM
- Subject is pregnant or anticipates becoming pregnant in the next 4 months.
- Subject anticipates moving within the next 4 months.
- Treating physician, for any reason, considering their patient inappropriate for the study, like uncontrolled bipolar disease

6.5 Concomitant Medications

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications, and supplements.

6.5.1 Prohibited Medications and Treatments

Patients will be excluded if currently taking a chronic medication that would interfere with metabolic control, such as prednisone. Patients will be excluded if currently taking any diabetes medication prior to enrollment in the study. They will be allowed to continue if treatment is started after enrollment, but will be documented.

7 STUDY TREATMENTS

7.1.1 Method of Assigning Subjects to Treatment Groups

2:1 Randomization; in previous studies baseline metrics have not been found to influence outcome, other than very high A1c, which is not applicable to this study.

7.2 Description of GEM

The 4-chapter GEM paper guide provides: 1) decisive didactic information about the effects of net carbohydrate consumption and routine physical activity on blood glucose fluctuations; 2) instructions to systematically use CGM feedback to ***educate*** them about how carbohydrates and physical activity impact *their* BG excursions, ***motivate*** them to repeat choices that lead to lower AUC, ***activate*** them to take steps to lower their BG elevations when detected by the high glucose alarm, and ***investigate*** the BG impact of new food and activity choices concerning their effect on their BG; 3) employ structured self-monitoring (diary) to organize and identify personal patterns in their food and physical choices that impact their AUC, and 4) automated personalized daily text messages to encourage engagement in a GEM lifestyle.

7.3 Devices

The FreeStyle Libre 2 Flash Glucose Monitoring System is a continuous glucose monitoring (CGM) device with real time alarms capability indicated for the management of diabetes in persons age 4 and older. It is intended to replace blood glucose testing for diabetes treatment decisions, unless otherwise indicated. The System also detects trends and tracks patterns and aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments. Interpretation of the System readings should be based on the glucose trends and several sequential readings over time. The System is also intended to autonomously communicate with digitally connected devices. The System can be used alone or in conjunction with these digitally connected devices where the user manually controls actions for therapy decisions.

Use of the FreeStyle Libre 2 Flash Glucose Monitoring System in this protocol complies with the requirements for a non-significant risk study under 21 CFR 812.3(m). It is not an implantable device, it is not represented to support or sustain human life, is not for use in diagnosing, curing, mitigating or treating disease and use of the device does not present a serious risk to study subjects. It is stored at room temperature.

The FitBit Activity Monitor is an FDA cleared device that will be used in this study to measure outcome data. It is stored at room temperature.

8 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1. To allow for individualized learning styles, a participant may choose to conduct the “Review

the GEM manual and Read Chapter One" at a different time than the rest of the GEM Start Visit, but within 1 week of the GEM Start Visit.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization will be signed and dated by the subject.

8.1 Clinical Assessments

8.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at baseline and post-intervention, and at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

8.1.2 Demographics

Demographic information (will be recorded at Visit 1 (Consent and baseline):

- date of birth
- sex
- race
- address
- email
- phone number

8.2 Medical History

Relevant medical history, including history of current disease will be recorded at Visit 1 (Consent and baseline).

8.3 Clinical Assessments

- CGM metrics including time >120 and GV
    - CGM will be fully blinded to the participant, unless on GEM so they may assess lifestyle modifications, and used to collect baseline and primary outcome data in a manner that will not bias RC subjects' activity as the CGM is programmed not to display values, only record values
- Height/Weight and BMI
- Blood pressure
- A1C
- Total cholesterol
- Triglycerides
- HDL
- LDL
- Presence of Atrial fibrillation
- Comprehensive proteomics

8.4 Psychological Assessments

- Health Questionnaires (PHQ-8)-measures depression
- Modified Diabetes Knowledge Scale
- Modified Diabetes Empowerment Scale
- Modified Treatment optimization scale
- Motivation and Attitudes Toward Changing Health Scale (MATCH)

8.5 Behavioral Assessments

- Carbohydrate Routine Consumption Scale
- Activity monitor that measures sedentary behavior, total steps and minutes of moderate to vigorous physical activity

8.6 Other Assessments

- Program Importance Questionnaire

8.7 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment and relation to intervention will be recorded on the case report form (CRF).

9 EVALUATIONS BY VISIT

There will be a baseline assessment, then a 1-month treatment period, followed by a 4.5-month post assessment (see Figure).

9.1 Prescreening and PCP Approval

1. Prescreen via phone call
2. If eligible after phone call, send HIPAA-A form
3. Once HIPAA-A is returned to study team, send letter to PCP regarding approval for participation
4. Once PCP approval is received, call participant to schedule Visit 1

9.2 Visit 1: Consent and Baseline (all subjects)

1. Obtain written informed consent
2. Record appropriate demographics, medical history, and concomitant medications
3. Perform clinical assessments
4. Collect fingerstick A1c using DCA Vantage A1c machine to confirm eligibility. If participant is ineligible they will be informed and asked if they would like to be contacted for future prediabetes or diabetes studies. If

yes, they will be offered the Opportunity to join the Primary Care Diabetes Lab patient registry. If patient is eligible, then:

   a. Collect blood for clinical laboratory tests, including A1c and proteomics
   b. Place blinded CGM and blinded activity monitor
   c. Configure participant activity monitor app for blinded data capture and connect to study team account
   d. Perform psychological assessments
   e. Perform behavioral assessments
   f. Randomization (results blinded to participant) after the above steps completed
   g. Schedule GEM Start visit (for participants randomized to intervention).
   h. Schedule RC start (for participants randomized to RC)

5. If the DCA Vantage A1c machine is not available or participant prefers venipuncture then blood will be collected for clinical laboratory tests, including proteomics and eligibility will be confirmed with A1c results prior to steps b-h above

If eligible, Visit 2 will be scheduled via phone call. If ineligible, participant will be informed and will be asked if they would like to be contacted for future prediabetes or diabetes studies. If yes, they will be offered the opportunity to join the Primary Care Diabetes Lab patient registry.

We will reach out to participants who are ineligible some time after their initial screening visit to see if they would like to come back in for a re-screen to repeat labs and/or the POC A1c test to see if they now qualify. All other procedures will remain the same.

9.3 Visit 2- Secondary Baseline (All subjects who are not able to confirm eligibility at Visit 1 will return for this Visit. If eligibility confirmed at Visit 1 then these steps are completed at that time.)

1. Place blinded CGM and blinded activity monitor
2. Configure participant activity monitor app for blinded data capture and connect to study team account
3. Randomization (result blinded to participant)
4. Perform psychological assessments
5. Perform behavioral assessments
6. Randomization (result blinded to participant). Randomization will not occur until steps 1-5 have been completed.
7. Schedule GEM Start visit (for participants randomized to intervention)
8. Schedule RC Start visit (for participants randomized to RC)

9.4 Visit 2/3– Start

9.4.1 RC Start (for participants randomized to RC), at least and as close as practical to 14 days following Secondary Baseline visit

1. History review, assess for AEs since last visit
2. Notify participant of randomization to RC
3. Blinded CGM data acquisition
4. Collect activity monitor
5. Schedule Follow Up visit for 4.5 months later (+/-2 weeks)
6. Schedule reminder contact for 2 weeks before next Visit; during contact, ask about interest in GEM if eligible

9.4.2 GEM Start (GEM subjects only)

1. History review, assess for AEs since last visit
2. Notify participant of randomization to GEM
3. Blinded CGM data acquisition
4. Instruct participant on unblinded Freestyle Libre 2 CGM
    a. Instruct on placement, use, strongly encourage scanning 20-40 times a day, but at a minimum scanning at least every 8 hours
    b. Establish participant account
    c. Connect to study account
5. Instruct participant on activity monitor
    a. Instruct on use
    b. Reconfigure smartphone settings to unblind activity date
    c. Verify participant account connection to study account
6. Review the GEM manual and read Unit 1 to ensure the participant understands the program. Encourage to complete 4 daily diary logs. Encourage significant other (if applicable) to also be present. Document whether significant other is present. To accommodate individual learning styles this may be done anytime within 1 week of the GEM Start Visit.
7. Set up text messaging (content, timing, frequency)
8. Schedule follow-up contact 2 weeks and 6 weeks later (when probability of dropout from lifestyle intervention peaks). Assess satisfaction with text messaging and change content/timing/frequency if necessary (and document).
9. Schedule Follow-up Visit for 4.5 months later (+/-2 weeks)
10. Schedule reminder contact for 2 weeks before next Visit; at that time, contact participant to assure they have a Libre 2 sensor inserted to collect the 14 days of end of study data.

9.5 Visit 3/4 – Study Period 1 End

9.5.1 RC End (All subjects)

1. History review, assess for AEs since last visit
2. Give participant blinded CGM sensor and activity monitor and instruction for returning devices via mail if not doing GEM.
3. Perform clinical assessments
4. Perform psychological assessments
5. Perform behavioral assessments
6. Collect blood for clinical laboratory tests, including proteomics
7. Assess interest/appropriateness of crossing over to GEM
    a. If crossing over to GEM, proceed to schedule visit 5 once A1c is confirmed via phone call.
    b. If not crossing over to GEM, participation complete once CGMs returned via mail.

9.5.2 GEM End (Study Period 1 End)

1. History review, assess for AEs since last visit
2. Perform clinical assessments
3. Download CGM data
4. Perform clinical assessments
5. Perform psychological assessments

6. Perform behavioral assessments
7. Complete Program Importance Scale
8. Collect blood for clinical laboratory tests, including proteomics
9. Place blinded CGM and activity monitor and instruct on how to mail back blinded CGM.

9.6 Visit 4/5- Study Period 2 Start

1. History review, assess for AEs since last visit
2. Blinded CGM data acquisition
3. Instruct participant on unblinded Freestyle Libre 2 CGM
    a. Instruct on placement, use, strongly encourage scanning 20-40 times a day, but at a minimum scanning at least every 8 hours
    b. Ensure participant account is working
    c. Connect to study account
4. Instruct participant on activity monitor
    a. Instruct on use
    b. Reconfigure smartphone settings to unblind activity date
    c. Verify participant account connection to study account
5. Review the GEM manual and read Unit 1 to ensure the participant understands the program. Encourage to complete 4 daily diary logs. Encourage significant other (if applicable) to also be present. Document whether significant other is present. To accommodate individual learning styles this may be done anytime within 1 week of the GEM Start Visit.
6. Set up text messaging (content, timing, frequency)
7. Schedule follow-up contact 2 weeks and 6 weeks later (when probability of dropout from lifestyle intervention peaks). Assess satisfaction with text messaging and change content/timing/frequency if necessary (and document).
8. Schedule Follow-up Visit for 4.5 months later (+/-2 weeks)
9. Schedule reminder contact for 2 weeks before next Visit; at that time, contact participant to assure they have a Libre 2 sensor inserted to collect the 14 days of end of study data.
10. Optional: For any participant coming off of the intervention, they will be asked at the end of the study visit 4 or 6, or contacted by email, phone, and/or letter to discuss if they would like to complete a short, semi-structured interview via audio and/or audio and video to provide feedback on the intervention to assist in improvements with the program for future studies. The interviews will be recorded and participants will be made aware of this. If any PHI is mentioned during the interview, it will be removed during the transcription process. This part is not required as part of the intervention and will not affect compensation or any study procedures.

9.7 Visit 5/6- Study Period 2 End

9.7.1 GEM End (Study Period 2 End)

10. History review, assess for AEs since last visit
11. Download CGM data
12. Perform clinical assessments
13. Perform psychological assessments
14. Perform behavioral assessments
15. Complete Program Importance Scale

16. Collect blood for clinical laboratory tests, including proteomics
17. Place blinded CGM and activity monitor and instruct on how to mail back blinded CGM.
18. Optional: For any participant coming off of the intervention, they will be asked at the end of the study visit 4 or 6, or contacted by email, phone, and/or letter to discuss if they would like to complete a short, semi-structured interview via audio and/or audio and video to provide feedback on the intervention to assist in improvements with the program for future studies. The interviews will be recorded and participants will be made aware of this. If any PHI is mentioned during the interview, it will be removed during the transcription process. This part is not required as part of the intervention and will not affect compensation or any study procedures.

9.5 Early Withdrawal Visit. A participant may withdraw from the study at ay time and will be given the opportunity to meet with the PI if desired. Multiple attempts will be made to schedule the participant for an early withdrawal visit to perform assessments and review any AEs.

10 SAFETY EVENTS REPORTING AND DOCUMENTATION

10.1 **Adverse Events**. Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). Adverse events will be recorded in the participant CRF. Adverse events will be described by duration (start and stop dates), severity, outcome, treatment and relation to study intervention, or if unrelated, the cause.

10.1.1 AE Severity. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

10.1.2 Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

10.1.3 AE Relationship to Intervention. The relationship of an AE to the study intervention should be assessed using the following the guidelines in Table 2.

10.1.4 Table 2. AE Relationship to Study Intervention

Relationship	Comment
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals.
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Possibly	There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
Unlikely to be related	A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
Not related	The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

10.2 Serious Adverse Events (SAE)

An SAE is defined as any AE that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

10.2.1 Serious Adverse Experience Reporting

Study site will document all SAEs that occur (whether or not related to study intervention) per local requirements. Any urgent reporting will be done within the acceptable perameters and timeline to all necessary reporting agencies. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study

visit have been completed. In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

10.3 Protocol Defined Events of Interest Requiring Real-Time Reporting

This study poses no greater than minimal risk and real-time reporting is not necessary.

10.4 Study Discontinuation

10.4.1 Early Discontinuation of Study Intervention

A subject may be discontinued from study treatment at any time if the subject or the investigator feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Pregnancy

If a subject is withdrawn from treatment due to an adverse event, the subject will be directed to obtain treatment, if necessary, by their primary care provider until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should be offered an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. Refer to study evaluations for early termination procedures.

10.4.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject or the investigator feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to the follow- up visit) should be offered an early discontinuation visit. Refer to Section 10 for early termination procedures.

10.4.3 Replacement of Subjects

Subjects who withdraw from the study will not be replaced.

10.5 Protocol Deviations

A protocol deviation is defined as any change, deviation, or departure from the study design or procedures of a research project that is NOT approved by the institution's IRB prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. These protocol violations may be major or minor violations.

The PI will use continuous vigilance to identify and report deviations.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the Investigator. A copy of the form will be filed in the site's regulatory binder.

11 STATISTICAL METHODS AND CONSIDERATIONS

The primary analyses will be a 2 (group) X 1 (change pre to post assessment) analysis of covariance analyzing change variables, with baseline variables serving as co-variants. The Benjamini-Hochberg procedure [31] will be employed to control for multiple comparisons. Exploratory correlational analyses will be performed to determine significance of baseline and change variable relationship to primary outcome variable. Analyses will be conducted in SAS v. 9.4. Statistical analysis of de-identified data will be completed at the University of Virginia. The University of Virginia has done all statistical analysis for previous GEM studies.

11.1 Data Sets Analyzed

- All randomized subjects will be included in analysis

11.2 Demographic and Baseline Characteristics

Descriptive statistics will be conducted to assess demographic and baseline characteristics.

11.3 Analysis of Primary Endpoint

The proposed study is a 2 between (groups) x 2 within (pre-post) partial cross-over randomized clinical trial. The primary endpoint of % glucose <120 will be compared between groups for study period 1 using t-tests; within the cross-over group for study period 2 using paired t-tests..

11.4 Analysis of Secondary Endpoints

Secondary outcome variables will be analyzed with standardized statistical methods for each variable type used to evaluate individual proteins and protein pathways. Correlations will be examined comparing data obtained from proteomic analyses, clinical measurements, and glucose excursion parameters. Data from participants will be compared to themselves to identify changes as a function of glucose control. Data will also be analyzed for groups of individuals by comparing the means and standard errors of the mean.

11. DATA COLLECTION, RETENTION AND MONITORING

Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study intervention.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents, but will be identified by a subject number and initials.

For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. *For paper CRFs:* If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

12.1 Data Management Procedures

The data will be entered into a validated database. All procedures for the handling and analysis of data will be conducted using good computing practices and HIPAA compliant software.

12.2 Archiving of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained.

12.3 Availability and Retention of Investigational Records

Record retention will be in accord with 21 CFR 312.62 and HIPAA regulations.

12.4 Subject Confidentiality

In order to maintain subject confidentiality, only a subject number and subject initials will identify all study subjects on CRFs and other documentation.

Participant confidentiality and privacy are strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. Consents will be maintained in a confidential manner in accordance with the code of federal regulations and HIPAA.

13 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50) and Institutional Review Boards (21 CFR 56.)

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. Participant Binders will be kept in a locked cabinet or HIPAA compliant e-binder. Clinical information will not be released without written permission of the subject. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

13.1 Protocol Amendments

Any amendment to the protocol will be written by the investigator. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to participants. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately, provided the IRBs are notified within five working days.

13.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB prior to study initiation. Serious adverse events regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning participant recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the participants or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse events occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the participants of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

13.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

Once a potential subject is identified, they will be interviewed in a quiet and private place and may have family or friends with them if they choose. If there is concern that the potential subject may not be able to read, the potential subject will be asked to read the first sentence of the consent form to determine if they are capable of reading. Depending on the response, they will either be offered the opportunity to read the consent form or have the consent form read to them. Once the consent has been read the person obtaining consent will summarize the consent form verbally, asking open ended questions to determine if the potential subject understands what is being covered in the consent form. Questions might include:

- Would you summarize for me what you believe will be done to you if you are in this study?
- Would you benefit from this study?
- What do you feel are the risks of being in this study?

Potential subjects will be given an opportunity to ask questions. Their level of understanding will dictate how much time will be spent covering each item. Once all of their questions have been answered, if they decide to participate, they will be asked to sign the consent form. The person obtaining consent will sign the form and subjects will be given a copy of the signed consent form. Study procedures can then begin. The informed consent process for each individual subject will be documented in the subject's record.

13.4 Publications

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

14 APPENDIX 1. SCHEDULE OF EVENTS

	VISIT 1: BASELINE (ALL GROUPS)	VISIT 2: SECONDARY BASELINE (THOSE UNABLE TO HAVE ELIGIBILITY CONFIRMED AT V1)	VISIT 2/3: START RC OR GEM 14 DAYS +/- 2 DAYS	VISIT 3/4: 4.5 MONTHS +/-2 WEEKS		VISIT 4/5: CROSSOVER RC GROUP START GEM 14 DAYS +/- 2 DAYS	VISIT 5/6: CROSSOVER RC GROUP END GEM 4.5 MONTHS +/-2 WEEKS
				GEM END	RC END		
Informed Consent	X						
Randomization	X¤	X¥					
Medical History; Verify Eligibility	X	X¥	X	X	X	X†	X
Clinical Labs/Assessments	X			X	X		X
Questionnaires/ Scales	X¤	X¥		X	X		X
Set up text messaging			GEM Group			X†	
Place Blinded CGM and Activity Monitor	X¤	X¥		X	X		X
Place Unblinded CGM and Activity Monitor and train on use			GEM Group			X†	
Read and follow GEM Manual			GEM Group			X†	
Proteomics	X			X	X		X
Glucose and activity monitor setup, training			GEM Group			X†	
Use CGM and activity monitors			GEM Group			X†	
Final Visit/Study End				X*	X‡		X

*if randomized to GEM group at Visit 1

†if still eligible for GEM and agreeable to continuing study and to receiving GEM intervention

‡if no longer eligible for GEM or not agreeable to continuing study or to receiving GEM intervention

¤if able to confirm eligibility at time of V1

¥if unable to confirm eligibility at time of V1

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